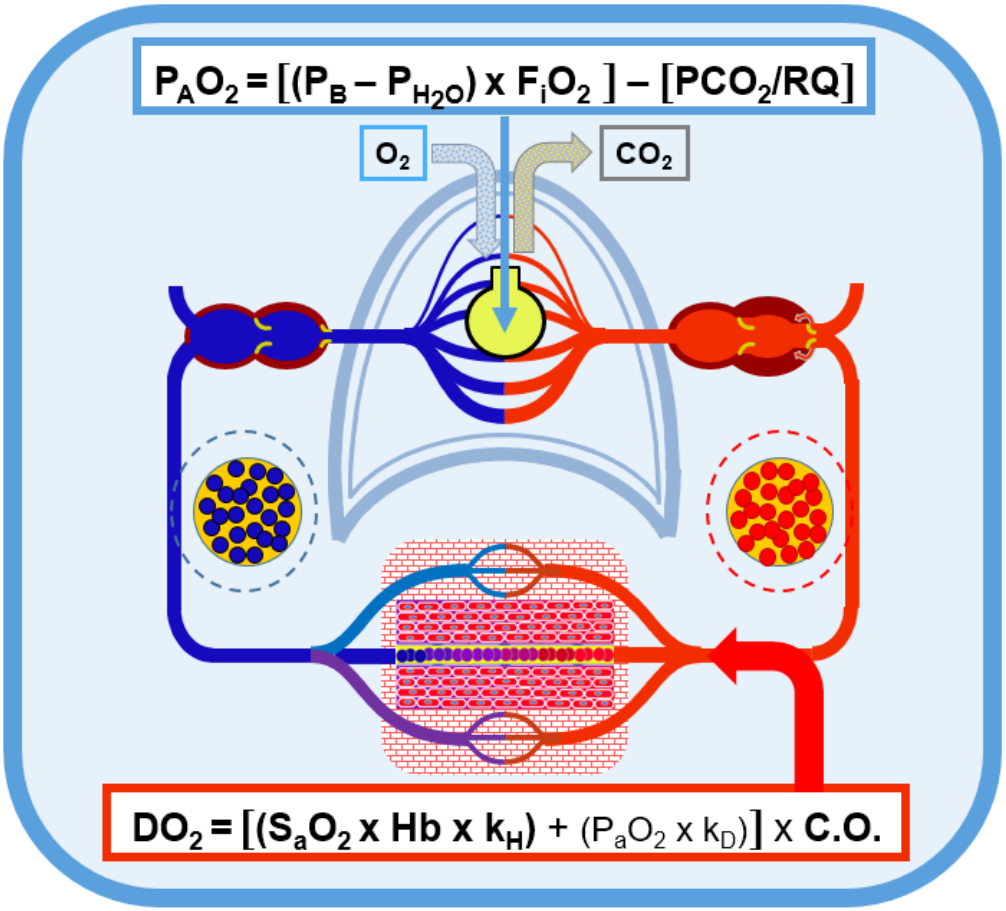
THE O_2 COMPENDIUM

THE PATHWAY OF OXYGEN TRANSPORT
FROM INSPIRED GAS TO TISSUE METABOLISM
IN HEALTH AND DISEASE

PLUS

THE ACID-BASE BALANCE AND
ITS IMPACT ON OXYGEN TRANSPORT



A COMPENDIUM FOR THOSE WHO WONDER

WHY

HELGE OPDAHL MD PhD

THE O_2 COMPENDIUM LAYOUT

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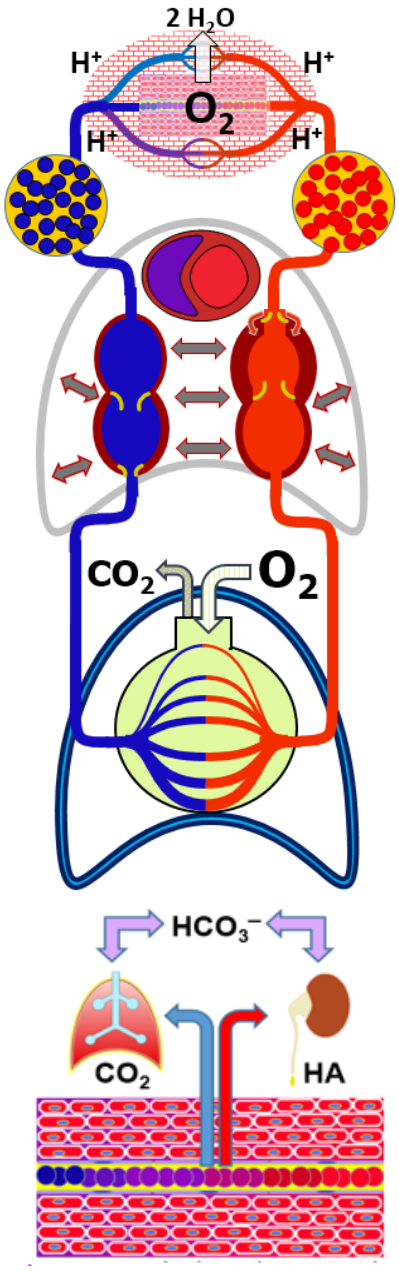

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Navigation: Clicking on blue text words jumps to pages where additional information or details, or pertinent figures are presented. In addition, the *search* function (🔍) for key words or phrases in Adobe Reader® can identify additional locations of topics of interest. Clicking on *reference* numbers in the text jumps to the pertinent reference, clicking on cross-references jumps to the location of the original reference number. To jump back to the previous position, shortcuts are **Alt+left arrow** in **Windows**, alternatives in **MacOS** are ↑+⌘+**8** *or* ⌘+**]**.

ABOUT THIS COMPENDIUM

Normal function of human tissue cells, as well as their survival, can only be sustained by oxygen-dependent (aerobic) metabolism; failure of O_2 supply may develop rapidly in acute disease and trauma and lead to severe tissue damage or death. It is a feared complication during surgery, anesthesia and postoperatively; prompt interventions can, in many instances, reverse or ameliorate both the failure and its consequences. A prerequisite for interventions to be successful is correct identification of the origin(s) of failure. Such identification requires understanding of *i)* the physiological mechanisms involved in normal O_2 transport and *ii)* the consequences of anatomical and pathophysiological changes in the involved organ systems.

The intention behind compilation and publication of this compendium is to present information pertaining to O_2 transport and metabolism in one easily accessible source, with the hope of enhancing the ability of clinicians to identify sources of oxygenation problems and thus choose optimal therapeutic strategies. The compendium portrays *i)* the normal function of molecules, cells and organs involved in the transport of O_2 from inhaled gas to the mitochondria of tissue cells, and *ii)* the various changes in their function that may compromise aerobic metabolism. The basic principles behind common therapeutic options related to organ dysfunction are reviewed.

The primary target audiences are *junior doctors* and *nurse specialists* working within fields of medicine where patients may develop failure of tissue oxygenation acutely, and who wish to attain an understanding of pathophysiological principles for diagnosis and treatment beyond algorithms. Other groups of medical or paramedical personnel involved in treatment and care of persons with oxygenation problems may also find some parts to be of interest.

In severely ill patients with tissue oxygenation problems, the acid-base balance is often disturbed. Such disturbances may change the conditions for O_2 delivery to the tissue cells in a positive or negative direction, depending on interactions between pulmonary and circulatory function and the blood hemoglobin. A part of the compendium therefore deals with normal acid-base conditions, pathological deviations, and their consequences for the O_2 transport.

The selection of topics and extent of details is influenced by the author's background in anesthesia, emergency- and intensive care medicine, teaching and research. An outline of major topics, and how the compendium is organized, is displayed on the previous page. References are listed separately for each part, resulting in some duplicates. As the compendium focuses only on aspects of organ function important for tissue O_2 supply, it is no substitute for textbooks with a wider pathophysiological scope.

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PART 1. HUMAN OXYGEN TRANSPORT AND UTILIZATION; ASPECTS OF ACID-BASE BALANCE

A SHORT OVERVIEW FOR THE NON-SPECIALIST

GENERAL INTRODUCTION.

- **An oxygen (O_2) dependent, aerobic metabolism** is necessary for generation of the amount of energy required for normal tissue cell function. The combustion of nutrients produces a surplus of electrons (e^-); a continuous creation of energy depends on the transfer of these to oxygen molecules (a *reduction* of oxygen), effected by the enzymes constituting the *mitochondrial electron transport* - or *respiratory chain.* The reduced oxygen then combines with H^+ ions dissolved in the aquatic fluids of the body to create water (H_2O) as the end product. Another end product is carbon dioxide gas (CO_2), the result of a complete aerobic combustion of carbohydrates. To sustain aerobic metabolism,

i) An adequate supply of **molecular O_2** must be available to the mitochondria,
ii) The function of the **electron transport chain** (Part 2-1) must be intact, *and*
iii) The organism must be able to **excrete the end products** of tissue metabolism.

- **The O_2 supply to the tissue cells** is determined by the **flow of blood** through the tissue microcirculation and the **O_2 content** of the arterial blood **(C_aO_2)** (Part 2-3).
  - The tissue blood flow is a function of the *local* **perfusion pressure** (i.e. the arterial minus venous pressure) and is modified by the local **tissue resistance** to flow. The *general* perfusion pressure is determined by the cardiac output (**C.O.**) and the systemic vascular resistance **(SVR)** (Part 3-1), and is modified by the local tissue resistance to flow.
  - The **C_aO_2** is primarily a function of the number of hemoglobin molecules **(Hb)** and their saturation with O_2 **(SO_2)**. Under normal conditions, the amount of O_2 dissolved as a gas in the arterial blood, measured as **PO_2** (in kPa or mmHg, see Apx) represents only 1-2% of the total C_aO_2 when Hb is in the normal range. A **simplified** calculation of **C_aO_2** can then be used for bedside purposes (see below and Part 2-3 for *accurate* calculations):

$C_aO_2 \approx k \times Hb \times S_aO_2/100$ where **k** (Hüfner's constant) defines **$mlO_2/gHb/dl$ blood.**

The delivery of O_2 (DO_2) to the whole organism is defined by the product of the arterial O_2 content (C_aO_2) and the flow of blood, i.e. the cardiac output (C.O.):

$DO_2 = C_aO_2 \times$ C.O.

Increased blood flow can compensate for substantial reductions in C_aO_2. In persons with normal cardio-circulatory function, even 50-60% reductions in C_aO_2 can be compensated for by increased blood flow. The opposite is possible only to a limited extent, augmenting the **Hb** levels require an increased erythrocyte mass which increases the viscosity of the blood, with negative effects on the C.O. as well as the microcirculatory blood flow (see below). Assumptions about what constitutes an **acceptable DO_2** in severely ill patients cannot focus on levels of **Hb**, **P_aO_2** and **S_aO_2** alone, but must include an individual estimate of the reserve capacity of the heart (i.e. the capacity for increasing the C.O.).

- **Re-oxygenation** of the blood occurs during passage through the **pulmonary capillaries**. When in close contact with the gas in the lung alveoli (Part 4-1), the O_2 pressure in capillary blood (P_cO_2) is equilibrated with that in alveolar gas (**P_AO_2**) before leaving the lungs. The O_2 taken up by the blood is replenished to the alveolar gas by an equal amount from the **inspired**

O_2. The inspired gas volumes, and thus the mass of inspired O_2, rapidly adapts to changes in metabolic rate and O_2 consumption (**$\dot{V}O_2$**). Even at maximal $\dot{V}O_2$, the P_AO_2 and thus the P_aO_2 of healthy persons stays normal.

- If the tissue O_2 supply fails, due to *insufficient perfusion* or *inadequate* C_aO_2, the cells must revert to O_2-independent (*anaerobic*) cellular metabolism (Part 2-1). The amount of energy generated then becomes too low to sustain normal cell function; the most O_2-dependent cells (brain, contracting myocardium) become dysfunctional within seconds (Part 2-4, Part 3-3). If adequate O_2 supply cannot be rapidly re-established, all human tissue cells ultimately succumb.

THE OXYGEN PATHWAY FROM AMBIENT AIR TO CELLULAR METABOLISM – A SCHEMATIC PORTRAYAL

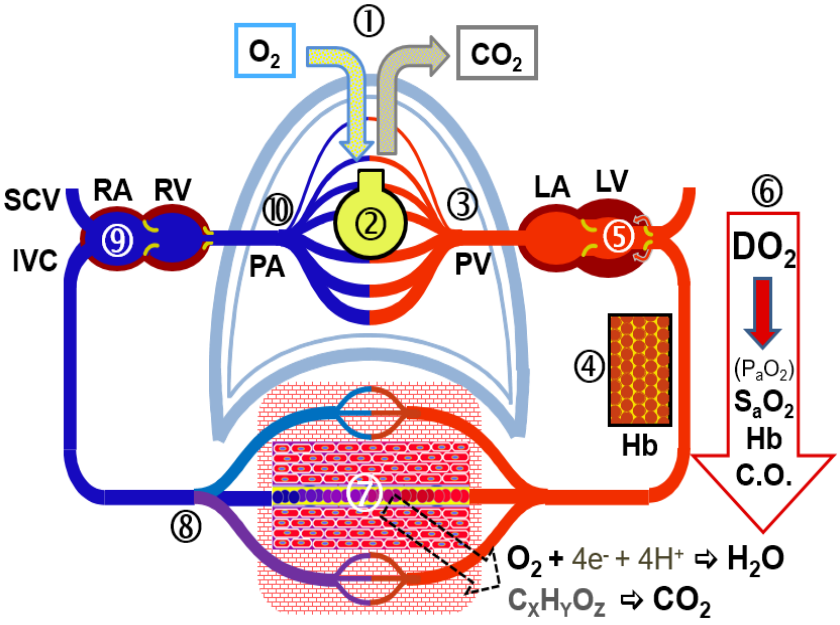

Figure 1-1. *Simplified drawing of the O_2 transport pathway, numbers correspond to the text paragraphs below. Abbreviations:* **SCV:** *Superior caval vein.* **ICV:** *Inferior caval vein.* **RA:** *Right atrium.* **RV:** *Right ventricle.* **PA:** *Pulmonary artery.* **PV:** *Pulmonary vein.* **LA:** *Left atrium.* **LV:** *Left ventricle.* **DO_2:** *Total O_2 delivery to the organism.*

A simplified overview of important elements in the oxygen transport pathway is depicted in fig. 1-1. This figure displays the *physiological* aspects of normal O_2 transport, but is *anatomically* incorrect and cannot demonstrate the interactions between the chambers of the heart (ventricular interdependence) or how changes in lung function and in intrathoracic pressures affect their performance. As such interactions are important for the O_2 transport, a description of such interactions, as well as of normal circulatory and pulmonary physiology and pathophysiology, are presented in Parts 3 and 4 of this compendium (see index of topics below).

① The oxygen content of the ambient air. See Part 4-1 for details.

- Ambient air consists mainly of a mixture of nitrogen (N_2) and oxygen (O_2) molecules, plus trace amounts of many other gases. In dry air, the **volume of O_2 gas,** and thus the number of O_2 molecules, represents about 20.9% (i.e. a fraction (**FO_2**) of 0.209) of the total gas volume. This fraction is *independent* of the actual barometric pressure.
- The **pressure** of O_2 gas (**PO_2**) is proportional to the ambient barometric pressure (**P_B**). The PO_2 of ambient air decreases with increasing altitude and increases below the ocean surface. The **PO_2 of dry air** at normal **sea level pressure** (101.3 kPa *or* 760 mmHg) is:

P_B x FO_2 =101.3 **kPa** x 0.209 = **21.2 kPa** *or*
760 **mmHg** x 0.209 = **158.8 mmHg**.

The addition of other gases or vapors to dry air dilutes it and thus displaces part of the O_2 molecules, reducing the O_2 fraction and thus the PO_2 of the inspired gas. In 100% humidified air at body temperature (37°C *or* 98.6°F), the H_2O vapor has a pressure of 6.3 kPa *or* 47 mmHg, the H_2O then represents 6.2% of the total number of gas molecules. The **PO_2 of 100% humidified air** at sea level pressure and body temperature is therefore

$(P_B - P_{H_2O}) \times FO_2$ = (101.3-6.3) **kPa** x 0.209 = **19.9 kPa** *or*
(760-47) **mmHg** x 0.209 = **149 mmHg**.

② **The oxygen content of the alveolar gas.** See Part 4-1 for details,

The continuous addition of O_2 *to* the blood, and excretion of CO_2 *from* it, occurs in the **alveolar-capillary unit**. The efficiency of this gas exchange is so great that even when the blood flow increases three to four times, the PO_2 and PCO_2 of the pulmonary capillary blood become equal to that of the alveolar gas *before* the blood leaves the alveoli. In a person with normal body mass and metabolism, the total O_2 consumption **($\dot{V}O_2$)** of a resting organism *at* normothermia is ≈250 mlO_2/min, and the total *production of CO_2* is ≈200 ml/min.

- The **gas volume in the lungs** at the end of a passive expiration (i.e. the sum of gas volumes in all alveoli) is around **2 500 – 3 000 ml** in a sitting person. This volume is close to the functional residual volume or -capacity **(FRC).** It communicates with the ambient gas through the **conducting airways**, where gas flows through but no gas exchange occurs. The gas volume in this conducting space, the **anatomical dead space**, is around **150 ml**. All pulmonary gas volumes vary with body size; the height is the most important factor. The FRC also varies with body position (Part 4-1).
- The main task of pulmonary ventilation is to replenish O_2 *to*, and excrete CO_2 *from*, the alveolar air at the same rate as they are consumed or produced, respectively, by the tissue metabolism. Under resting conditions, a **tidal volume** (V_T) of around **500 ml** with a rate of **10-12 breaths/min** is sufficient to keep the alveolar level of both gases stable. As the first 150 ml inhaled through the anatomical dead space consists of alveolar gas from the previous exhalation, the **effective volume of fresh gas** added to the alveolar gas with each breath is around **350 ml**.
- After humidification in the airways, the O_2 of the inspired air is further diluted by CO_2 after entering the alveolar space; the normal alveolar gas content of CO_2 is about 5.2% with a gas pressure of 5.3 kPa (40 mmHg). Hypoventilation affects both gases; if the amount of inspired O_2 fails to keep up with the amount consumed by the tissues, the alveolar PO_2 decreases and the PCO_2 increases simultaneously. In normal lungs, the level of arterial CO_2 can be used to predict the alveolar PO_2; under steady-state conditions, the mean pressure of O_2 within the alveoli (**P_AO_2**) can be calculated by the **Alveolar Gas equation**

$P_AO_2 = (P_B - P_{H_2O}) \times F_iO_2 - P_aCO_2/RQ$.

where **RQ** (the Respiratory Quotient) is the ratio between CO_2 production and O_2 consumption (normal value ≈ 0.8, Part 5-2). Inserting normal pressures gives:

P_AO_2 = (101.3 – 6.3) **kPa** x 0.209 – 5.3 kPa/0.8 ≈ **13.3 kPa** *or*
(760-47) **mmHg** x 0.209 – 40 mmHg/0.8 ≈ **100 mmHg**.

A major difference between the *calculated* **P_AO_2** and the *measured* arterial **PO_2 (P_aO_2)** indicate a dysfunction of the gas exchange in an increased number of alveolar-capillary units. Such calculations are, however, inaccurate in the presence of gases (other than CO_2) that displace O_2, and under extreme or unstable conditions with rapid shifts in P_B *or* ventilation.

- During strenuous muscular exertion, O_2 uptake and CO_2 generation may increase ten times or more (Part 2-1). The pulmonary capacity for adapting tidal volumes, respiratory rate, and pulmonary circulation to variations in metabolic rate is so great that the arterial concentrations of O_2 and CO_2 in persons with normal respiratory system remain stable during both increases and reductions in metabolism (Part 4-1).

③ The PO_2 of arterial blood and the O_2 content of the blood (C_aO_2).

See Part 2-3 and Part 4-1 for details.

- The amount of O_2 *dissolved* in blood at 37°C is only 0.0225 ml O_2 per kPa and dl blood, i.e. 0.3 mlO_2/dl in normal blood with a P_aO_2 of 13.3 kPa (100 mmHg). Almost all the O_2 molecules that leave the alveolar gas to become dissolved in the pulmonary capillary blood end up being bound to the Hb molecules inside the erythrocytes (fig. 1-2).

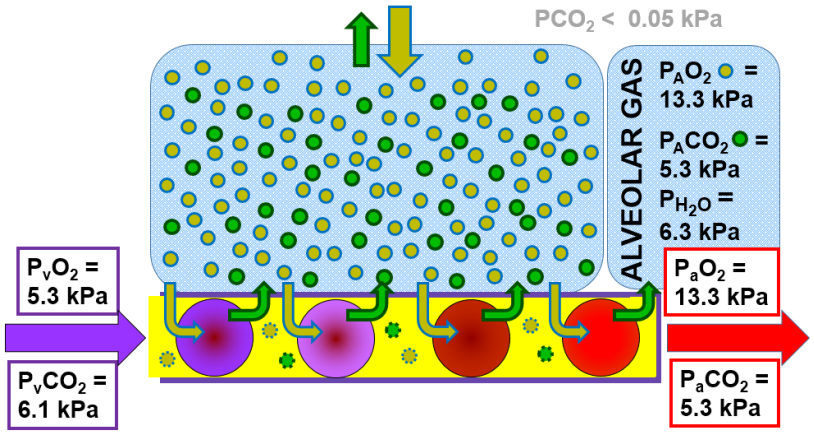

Figure 1-2. *Schematic depiction of the principles of gas exchange in the alveolar-capillary unit, with normal venous (left) and arterial (right) values. Arterial and alveolar pressures of O_2 and CO_2 become equal before the capillary blood leaves the gas-blood interface. A decrease in ventilation reduce both O_2 supply and CO_2 excretion simultaneously: the alveolar, and thus arterial, PO_2 falls and PCO_2 increases.*

- Each Hb molecule can bind four O_2 molecules, and each gram of Hb in normal blood binds 1.34 ml O_2 (*Hüfner's constant*) when *all* potential binding sites on *all* Hb molecules are occupied with O_2 (Part 2-3). In a sample of normal arterial blood with a P_aO_2 of 13.3 kPa, about 97.5% of all Hb molecules are saturated with O_2, usually given as the O_2 saturation (S_aO_2% *or* HbO_2).

The total O_2 content (**C_aO_2**) of 100 ml of normal arterial blood is calculated as

C_aO_2 = [(1.34 mlO_2/g x Hb g/dl x S_aO_2/100) + (P_aO_2 x 0.0225 mlO_2/dl/kPa*)]

(* for PO_2 when given in kPa, when given in mmHg, the constant is 0.003), see also *introduction* and Part 2-3 for a *simplified* version of the calculation.

Given normal values for persons with healthy lungs at sea level (Hb = 15 g/dl, S_aO_2= 97.5% and P_aO_2= 13.3 kPa), the equation becomes

C_aO_2 = [(**1.34** mlO_2/gHb x **15** g/dl x **97.5**/100) + (**13.3** kPa x **0.0225** mlO_2/kPa)] = [(**19.6** mlO_2) + (**0.3** mlO_2)] = **19.9** mlO_2/dl blood *or* close to **20 ml O_2**/dl blood.

- As the SO_2 cannot be higher than 100%, the above equation illustrates that increasing the P_aO_2 (by increasing the O_2 of the inspired gas) in persons with healthy lungs and an already normal S_aO_2 has only a modest effect on the C_aO_2 when Hb levels are in the normal range. The relationship between PO_2 and SO_2 is non-linear and forms a sigmoid curve, the HbO_2 dissociation curve (Part 2-3, fig 2-19). The shape and position of the curve, and thus the relationship between PO_2 and SO_2, is influenced by the intra-erythrocyte levels of pH, blood

temperature, 2,3 DPG content, and PCO_2 (Part 2-3, fig 2-20). Any change of these parameters affects the HbO_2 affinity and the S_aO_2 corresponding to a given P_aO_2, therefore also the **C_aO_2**.

- There is considerable variation in the ventilation as well as the perfusion in different parts of normal lungs. The arterial **PO_2** and **SO_2** represent the **weighted mean** of all fractions of blood draining the various parts of the lungs (Part 4-1).

④ The role of hemoglobin in oxygen transport. See Part 2-3 for details.

- The concentration of Hb molecules in the blood, as well as their O_2 saturation (S_aO_2), determine the O_2 content (C_aO_2) of the blood leaving the lungs (see above); an increase in the Hb level increases the C_aO_2 by approximately the same fraction.
- Under normal conditions, the Hb concentration is roughly proportional to the number of erythrocytes. Only the Hb molecules located *within the erythrocytes* are effective O_2 transporters, free Hb molecules dissolved in plasma do not readily release bound O_2 (Part 2-3). The number of erythrocytes has an important impact on blood viscosity, which affects both the pumping capacity of the heart and the microcirculatory flow conditions. In persons with cardiac dysfunction, increased Hb augments the viscosity and increases the resistance to left ventricular ejection, which may result in reduced stroke volumes.
- Hb thus has a Janus function in persons with reduced cardiac function. Increased Hb levels *raise the* C_aO_2 but may simultaneously *reduce blood flow* by opposing the left ventricular ejection. On the other hand, reduced Hb levels lower the C_aO_2 but also reduce the cardiac work and facilitate ejection of higher stroke volumes (see also ⑥ below).

⑤ Left ventricular (LV) function. See Part 3-1 for details.

In persons with normal hearts, the LV function determines the cardiac output (**C.O.**), i.e. the total amount of blood pumped by the LV into the aorta. The C.O. is the product of stroke volume (**SV**) and the heart rate (**HR**), i.e. **C.O. = SV x HR.** The relationship between the LV end-diastolic *filling volume*, the *force of contraction* and the *resistance to ejection* determines the stroke volume. The resting C.O. is 5-6 l/min in a western adult with normal body size.

- The **LV force of contraction** depends on
  - The end-diastolic **filling volume** (preload, Part 3-1), which is a function of the **filling pressure** *and* the **cardiac compliance**. The latter may be changed by factors *intrinsic* to the myocardium *or* by *external factors* that change the transmural filling pressures (e.g. changes in intrathoracic- and/or intra-pericardial pressure).
  - The **myocardial contractility**, i.e. the inherent contractile strength of the myocardial muscle fibers.
- The **resistance to ejection** of the stroke volume, which opposes the force of contraction, is mainly influenced by
  - The **systemic vascular** (arteriolar) **resistance (SVR)**,
  - The **elasticity** of the aorta and other large vessels.
  - The **viscosity** of the blood.

Arrhythmias, as well as dysfunction of the cardiac valves, reduce the efficiency of the LV function even when filling volumes and myocardial contractility *per se* are normal.

⑥ The global O_2 delivery to the organism (DO_2). See Part 2-3 for details.

- The DO_2 is a function of the O_2 content of the arterial blood (C_aO_2) and the C.O., and is calculated as **$DO_2 = C_aO_2$ x C.O.** Inserting normal values for **C_aO_2** and **C.O.** (≈ 200 mlO_2/l and ≈ 5 l/min, respectively), we get

DO_2 ≈ 200 mlO_2/l **x 5** l/min ≈ **1000 mlO_2/min**

of which 22-25% (about 250 mlO_2/min) is consumed by a resting organism (see above).

- Increases in C.O. can compensate for substantial reductions (50% or more) in C_aO_2. When the reduced C_aO_2 is due to falling Hb, the C.O. increase is facilitated by reduced blood viscosity. Increasing the C_aO_2 by increasing Hb (by transfusions) when the *primary* problem is a C.O. reduction has, on the other hand, little (or even negative) effects.
- The difference in O_2 content between arterial and mixed venous blood reflects the ratio between the O_2 consumption ($\dot{V}O_2$) of the organism and the DO_2 (the $\dot{V}O_2/DO_2$ ratio is the O_2 *extraction* ratio or -fraction); this ratio indicate to which degree the DO_2 can be assumed to be adequate relative to the actual $\dot{V}O_2$.

⑦ Tissue consumption of O_2 ($\dot{V}O_2$). See Part 2-3 for details.

- Consumption of O_2 during the production of energy (aerobic metabolism) depends on the normal function of mitochondrial enzymes. Simultaneously, the metabolism of nutrients generates CO_2.
- During aerobic metabolism, the normal ratio between $\dot{V}O_2$ and CO_2 production is reasonably constant (1:0.8) as long as the relative concentration of nutrients in the blood remains stable. Increases and reductions of $\dot{V}O_2$ are accompanied by proportional changes in CO_2 production.
- Different tissues consume varying fractions of the O_2 supplied; the kidneys consume less than 10%, the brain about 33%, and the beating heart around 60-65%.

⑧ The O_2 content of venous blood. See Part 3-4 and Part 5-4 for details.

- The O_2 content of venous blood (C_VO_2) draining each organ is a weighted average of that in venous blood draining different areas of tissue within the organs. At rest, when about 22-25% of the O_2 supplied to the organism as a whole is consumed; the $\dot{V}O_2/DO_2$ ratio is then ≈ 0.25. The normal SO_2 in mixed venous blood (S_VO_2) entering the pulmonary artery is therefore around 72-75%.
- The C_VO_2 of the blood draining an organ, relative to C_aO_2 and blood flow, defines the O_2 consumption of the organ (Fick's principle). If samples of mixed venous blood, i.e. the weighted mean CO_2 from all organs, can be obtained (from the right ventricle or pulmonary artery, see below), the $\dot{V}O_2$ can be calculated using this principle (see also Part 3-4).
- Due to high blood flow and low O_2 consumption in the kidneys, the SO_2 in the inferior caval vein (ICV) is normally slightly higher (2-5%) than that in the superior (SCV) at rest. Increased O_2 consumption by contracting muscle groups, as well as circulatory changes induced by disease, may change this balance so that the SO_2 in SCV is higher (Part 5-4).

⑨ Venous return to the right atrium. See Part 3-1 for details.

- The main tasks of the right ventricle (RV) are to *i)* ensure optimal perfusion of the alveolar-capillary units, *and ii)* supply the left ventricle with an adequate volume of oxygenated blood. The function of the right ventricle is sensitive to changes in venous return; reduced filling of the right atrium (e.g. hypovolemia, vasodilation) lowers the stroke volume pumped by the right ventricle. Given normal resistance in the pulmonary vessels, compliance conditions and

function of the valves, the end-diastolic filling volumes of the right and left ventricle change in parallel, but their filling volumes and pressures are different.

- The right atrial filling pressure is an important, but not the only, determinant for the right ventricle end-diastolic filling volume. The central venous pressure (**CVP**) is, in most patients, representative of the RV filling pressure but *not* necessarily of the *RV filling volume*. For accurate calculation of the systemic vascular resistance (**SVR**), measurement of the CVP is necessary (see Part 3-1 for *bedside* simplification).
- If the RV compliance, as well as the intrathoracic and intrapericardial pressures, are normal, there is a rough *qualitative* relation between changes in filling pressures and – volumes. The *quantitative* precision is, however, low and changes in CVP may not reflect changes in the ventricular filling volumes in disease or during positive pressure ventilation (Part 3-1).

⑩ The O_2 in mixed venous blood, pulmonary vascular resistance.

- The *right atrium* receives venous blood from all tissues, including the myocardium; as the blood from SVC, IVC, and sinus coronaries are not perfectly mixed in the right atrium, the O_2 content of blood sampled from this site varies with the position of the orifice of the sampling catheter (Part 5-4).
- Pressures measured in the pulmonary artery (**PA**) indicate the resistance to ejection of the right ventricle stroke volume. For reliable calculation of the pulmonary vascular resistance (**PVR**), measurement of the pressure in the pulmonary veins (as pulmonary artery occlusion pressure, **PAOP** or **PCWP**) is also necessary (Part 3-1 and Part 4-1).

THE ACID-BASE BALANCE OF THE BODY (See Part 5 for details).

Aerobic as well as anaerobic metabolism generate acid metabolites; their concentrations in body fluids are under normal circumstances kept at low levels. Increased levels may be due to *increased production*, *reduced elimination*, or both. *Exogenous acids* may also become part of the body fluids. The *end-stage metabolites* (e.g. carbon dioxide, sulfuric- and phosphoric acid) must be excreted from the organism by the lungs and kidneys (fig. 1-3) while the *intermediate-stage* metabolites (e.g. lactic acid, keto acids) normally are utilized by endogenous metabolic processes. Increased levels of the latter may rapidly be normalized if the metabolic processes necessary for their further utilization are re-established. For the metabolic processes to continue unopposed, all types of metabolites must be eliminated at the same rate as their production. Failure to do so impedes the metabolic functions of the cells.

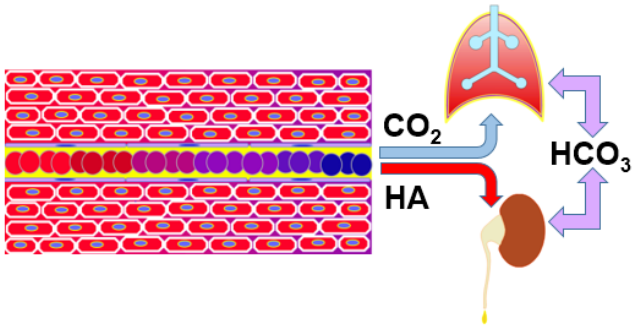

Figure 1-3. *End-stage acid metabolites from the tissue cells diffuse into the microcirculation and are excreted from the organism with the expired gas (carbon dioxide - CO_2) or the urine (sulfuric- and phosphoric acid - HA). The elimination or retention of bicarbonate buffer from the blood can be regulated by both lungs and kidneys.*

The acid-base conditions closest to those existing intracellularly are found in the microcirculation. The venous blood is therefore more representative for tissue acid-base conditions than arterial blood, as changes in the CO_2 elimination by the lungs affects the acid-base state in the latter. By convention, however, the acid-base status of patients are, in most clinical settings, based on samples of arterial or arterialized blood. To comply with this

practice, acid-base deviations in this compendium refer to conditions in arterial blood unless specified otherwise.

ACIDOSIS.

A change of the arterial blood concentration of hydrogen ions, **[H^+]**, to a level *above* 45 nanomol/l (i.e. 45 x 10^{-9} mol/l, corresponding to **pH** *below* 7.35) is defined as acidosis (see Part 5-1 and Apx). The four major causes of an excess **[H^+]** in the body fluids are

A. Failure to excrete end-stage acid metabolites from the body *at the same rate* as their generation by the tissues. Such acidosis are divided into

- **Respiratory acidosis,** where the acidosis is a result of a failure of the lungs to excrete *carbon dioxide* (CO_2) at the same rate as its production by the tissues. A new balance is established when the increased CO_2 content of the blood, and thus the alveolar air, cause more CO_2 to be excreted pr. ml of expired air.
- **Metabolic acidosis,** which is a result of a failure of the kidneys to excrete metabolic acids (e.g. *Sulfuric acid, Phosphoric acid*) at the same rate as their production **("renal acidosis").**

B. Pathological accumulation of normal acid intermediates creates **metabolic acidosis** when their rate of generation surpasses the body's capacity for further metabolism. Common causes are

- **Increased generation** of *lactic acid* (**lactacidosis)** due to an increased rate of glycolysis (e.g. strenuous exercise, high catecholamine levels) *or* a **decreased capacity fo**r its *further metabolism.* The latter may be due to inhibition of the mitochondrial electron transport chain (e.g. failure of O_2 supply, dysfunctional mitochondrial enzymes).
- **Increased metabolism of fats,** due to reduced availability of carbohydrates (e.g. diabetes, fasting/starvation) leads to accumulation of *keto acids* (**ketoacidosis**).

C. Pathological loss or dilution of base (increased loss of bicarbonate, HCO_3^-, from fistula or renal tubuli cells) *or* reduced concentrations of proteins with base properties (hemoglobin, albumin) may also result in **metabolic acidosis**.

D. Ingestion or infusion of exogenous substances that are acids, or are converted to acids by their metabolism (e.g. methanol to formic acid, ethylene glycol to oxalic acid).

ALKALOSIS.

A change in the arterial **[H^+]** to levels *below* 35 nanomol/l (corresponding to **pH** above 7.45) is defined as alkalosis. A deficit of **[H^+]** in body fluids of clinical importance may be the result of

A. Increased excretion of end-stage acid metabolites from the body at a rate surpassing their generation by the tissues.

- **Increased excretion of carbon dioxide** (CO_2) above its production rate leads to **respiratory alkalosis**. To obtain a new steady state between CO_2 production and excretion during hyperventilation, the alveolar air concentration of CO_2 is reduced.
- **Increased excretion of (H^+) ions by renal tubuli cells** (e.g. *loop diuretics, mineralocorticoid excess, tubuli cell dysfunction*) at a higher rate than their production leads to **metabolic ("renal") alkalosis**.

Other causes of **metabolic alkalosis** are

B. Increased loss of (H^+) ions from the GI tract (e.g. vomiting, gastric drainage, and diarrhea).

C. **Ingestion or infusion** of an excess of substances with base properties (e.g. milk, bicarbonate).
D. **Depletion of extracellular K^+** (which shifts increased amounts of H^+ *into* the cells).

BUFFERS.

Buffers in the human body are weak acids (e.g. carbonic acid, phosphoric acid) *and* protein molecules with a surplus of negatively charged amino acid side chains (e.g. hemoglobin, albumin). The buffers bond with excess H^+ ions within milliseconds when the **$[H^+]$** increase, and release them when the concentration decrease.

- The excess H^+ buffered by bicarbonate can subsequently be excreted from the body as CO_2 gas within seconds; reduced excretion of CO_2 retains more H^+ in the organism.
- The binding of excess H^+ by other buffers than bicarbonate is a temporary measure, keeping the concentration of free H^+ within narrow limits until renal compensatory mechanisms can eliminate the excess H^+ from the body (in acidosis) or reabsorb increased amounts of H^+ (in alkalosis).
- Loss of buffer favors an excess of $[H^+]$ and the creation of acidosis, an increased concentration of buffers favors a decrease in $[H^+]$ and the creation of alkalosis.
- As electroneutrality in body fluids must be maintained, changes in buffer concentrations are often accompanied by alterations in blood concentrations of K^+, Cl^-, and Na^+.

COMPENSATORY MECHANISMS.

- Compensation of metabolic acid-base disturbances in the form of increasing or decreasing ventilation and thus the excretion of CO_2 starts almost instantaneously (i.e. seconds to minutes) and has a *high capacity* for dealing with acute acid-base changes. Full compensation of acute disturbances does not occur instantaneously, due to the different functional properties of peripheral and central chemoreceptors (Part 4-1). In patients with limited ability to increase their ventilation, the capacity for compensating an acute metabolic acidosis is severely blunted.
- Compensation in the form of increasing or decreasing renal excretion of H^+ starts within minutes to hours, but has a *low capacity* and may need several days for full effect. In patients with renal dysfunction or failure, this compensatory mechanism is attenuated or lost.
- Due to the compensatory mechanisms, the relationship between the $[H^+]$ (measured as pH), bicarbonate, and PCO_2 levels differ between acute and chronic acid-base disturbances. These relationships may be further complicated if new, acute disturbances become superimposed on chronic conditions.

DIAGNOSIS OF ACID-BASE IMBALANCE.

- A *pH value alone* offers no clues as to whether the cause of the acid-base disturbance is due to respiratory (i.e. changes in CO_2 excretion *vs* production) or metabolic disturbances, *or* whether increased loss or accumulation of buffers are the culprit. Also, the arterial pH may be within normal range when renal compensation of a respiratory imbalance is complete, even if the underlying problem persists.
- Additional information, consisting of measurement of PCO_2 (with the calculation of bicarbonate), concentrations of blood electrolytes (e.g. K^+, Cl^- and Na^+) plus Hb and albumin will disclose the underlying mechanisms in most patients. In acidosis due to ingestion of unmeasured toxic alcohols, the difference between calculated and measured plasma osmolarity is a valuable additional tool (Apx).

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INTRODUCTION: PREREQUISITES FOR NORMAL HUMAN CELL FUNCTION.

A supply of energy derived from combustible nutrients is a prerequisite for all vital processes in the human organism. The energy requirements of the cells may broadly be grouped into

- **The energy required for cell survival,** i.e. the baseline quantity of energy needed to maintain the vital biochemical processes (e.g. transcellular transport of ions, substrates, and water, damage repair), *and*
- **The energy required for the performance of specialized functions**. Such specialized functions may be mechanical work (e.g. contraction of muscle fibers, movement of immunologically active cells), work of synthesis (e.g. production of signal molecules, serum proteins, and hormones), or the conduction and transfer of nervous impulses (e.g. peripheral nerves, central nervous system).

The main energy-generating metabolic processes in human tissue cells can be classed as

- **Anaerobic metabolism,** i.e. biochemical processes that function *without* an oxygen (O_2) supply. These processes represent the more **primitive part** of the inheritance from our ancestor cells (see below). They yield a modest amount of energy and cannot alone supply the energy necessary for normal function and survival of human tissue cells. Lactic acid is a major end product of anaerobic metabolism in human cells and the physiological end product in mature erythrocytes that survive with anaerobic metabolism (see Part 2-4).
- **Aerobic metabolism,** i.e. biochemical processes that require O_2 for their function; yields a much larger (approximately 20 times more) amount of energy and represent the more **sophisticated part** of the inheritance from our ancestor cells. In human aerobic metabolism, the major end products are H_2O (created when O_2 molecules combine with liberated electrons) *and* CO_2 (the end product of carbohydrate metabolism). The quantity of energy required for normal function of a given tissue depends on the tasks its cells must perform; the metabolic requirements of human tissue cells are so high that even baseline energy requirements cannot be sustained for long if the aerobic metabolic processes become inactivated.

Alternative evolutionary pathways in other types of organisms (e.g. some species of fish and turtles) have resulted in their ability to survive anoxia for weeks during hypothermic hibernation by inducing a change from aerobic to anaerobic metabolism (1). Short term hypoxia may also induce activation of factors (e.g. hypoxia inducible factor 1, HIF-1 α) that increase the tolerance of human cells to subsequent hypoxia episodes, but does not protect against prolonged hypoxia/anoxia.

For aerobic metabolism in the human organism to be possible, the fluid surrounding the cells (the interstitial fluid) must contain adequate amounts of dissolved O_2. To accomplish this, the blood perfusing the **tissue microcirculation** must be able to replenish the amount of O_2 continuously consumed by the cells on a second-to-second basis. The capacity for O_2 transport by the blood depends primarily on **flow conditions,** the **hemoglobin (Hb)** content, and its **saturation with O_2**; arterial blood with a normal Hb content contains about 75 times more O_2 per deciliter than the amount dissolved in plasma (see Part 2-3).

2-1. TISSUE OXYGEN REQUIREMENTS, MICROCIRCULATION

LIFE AND THE EVOLUTION OF AEROBIC METABOLISM

Life started under conditions where no, or only trace amounts, of O_2, were present on earth. Understanding the evolution of cellular functions may facilitate understanding of the way our cells work and their dependency on oxygen. The steps in the evolution of life, and subsequently the human organism (corresponding to symbols in fig. 2-1) may be summarized as:

⓪ Creation of the earth about 4.5 billion years ago – no O_2 present.
① First living cells gained their energy from anaerobic metabolism when no O_2 was present.
② First cells utilize photosynthesis for energy; generation of O_2 as a waste product.
③ First aerobic cells, with increased energy production possible through the utilization of O_2.
④ Rise of multicellular organisms.
⑤ First primitive animals (sponge-like creatures) 750 mill years ago (y.a.)
⑥ More complex animals 400 mill y.a.
⑦ Period with atmospheric PO_2 above today's levels, with giant insects 2-300 mill y.a.
⑧ Mammals ≈ 300 mill y.a, pre-humans ≈ 60 mill y.a, early humans ≈ 7-4 mill y.a.

Precursors to the human cells

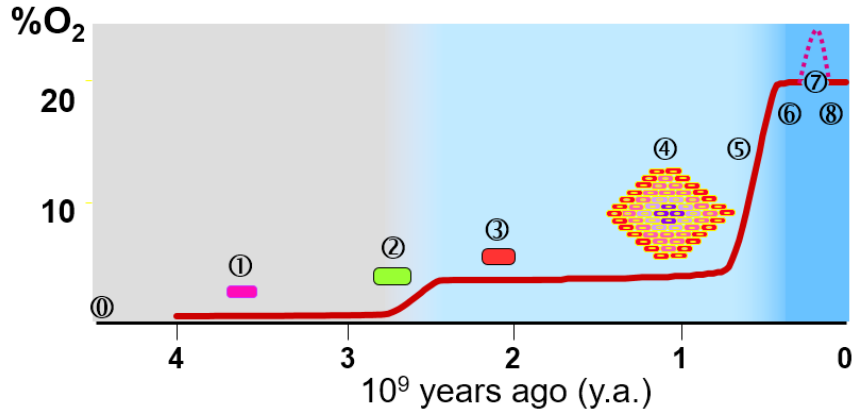

Figure 2-1. *Graph showing the evolution of atmospheric oxygen (Y axis) and various life forms as a function of time (X axis) after creation of the earth. See text above or symbols.*

The cells of our body are descendants of the first living cells (2). The assumptions about the early evolution of cells, and their subsequent progression to primitive organisms, are built on fossils, geological data, and genetics. Needless to say, timelines for this process are approximations.

Life started without oxygen.

The earth is probably about 4.5 billion years old (created about 9.2 billion years after "The Big Bang" formed the universe) and the *first cells* presumably came into being in shallow ponds of parts of the primeval ocean about 3.5 billion years ago. At that time, no O_2 (or only trace quantities) was present in the primeval ocean or the atmosphere (3, 4), see fig. 2-1. The ocean contained, however, molecules (substrates) that could liberate energy during various chemical degradation processes. The enzyme systems of the primitive cells could bring about a partial breakdown of such molecules by *anaerobic* (O_2-independent *metabolism*, *fermentation,* or *breakdown of chemical substances*); some of these metabolic processes were similar to those found in many types of primitive microorganisms (e.g. anaerobic bacteria, fungi, and yeasts) today. The energy liberated by such partial breakdown was sufficient for the first primitive cells, allowing them to thrive and multiply.

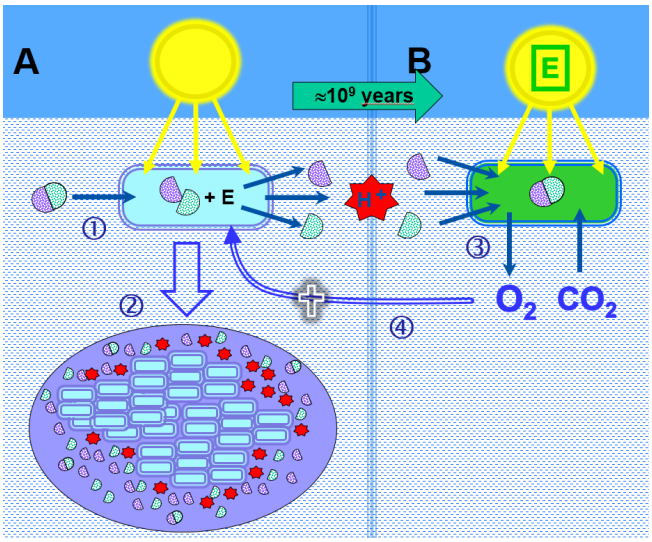

Figure 2-2. Panel A. *Primitive cells had a simple metabolism, which could utilize only a small part of the potential energy of the surrounding nutrients* ①. *As they multiplied* ②, *the concentration of nutrients decreased and that of waste products increased.*
Panel B. *Photosynthetic cells* ③ *could use some of the waste product for synthesis of new nutrients in metabolic processes driven by energy* (E) *from the sunlight. Their major waste product,* O_2, *was toxic* ④ *to most of the primitive cells.*

The continuous breakdown of complex molecules results in the accumulation of waste products. Anaerobic breakdown of nutrients resulted in the accumulation of various acids, such as lactic acid, or alcohols; these were excreted by the cells into the surrounding fluid. For the energy-liberating chemical reactions to continue unopposed, the concentration of these metabolic end products in the fluid surrounding the cells had to be kept low, this was effectuated by removal through dilution and convective transport. The prerequisites for this type of primitive metabolism to function was therefore

- Substrates (i.e. molecules) that could liberate energy during degradation by the cellular enzymatic system had to be available in sufficient concentrations in the fluid outside the cells.
- The substrates had to be able to cross the cell membrane to be exposed to the cell's enzymatic machinery.
- The waste products from the substrate metabolism could be removed efficiently from the cells, and subsequently from the fluid surrounding them.

The primeval ocean was large, while the initial primitive cells were few. To begin with, access to nutritious substrates was therefore in principle unlimited, and the waste products were quickly diluted and disappeared out into the primeval ocean. If the primitive cells reproduced themselves as rapidly as some bacteria do today (E. Coli bacteria can, under optimal conditions, divide every 15-20th minute (5, 6)), the number of cells in the most favorable locations would increase rapidly – one cell becoming up to approximately 34 billion (34×10^9) in 12 hours. As the number of cells, and thus also the mass of enzymes involved in the degradation processes, increased, the quantity of nutritious substrate in the water surrounding them decreased (fig. 2-2A). Simultaneously, the concentration of waste products increased; in a closed environment, such conditions lead to diminished cell growth and multiplication, and eventually to cell death.

Photosynthesis – a source of nutrients and oxygen.

About 2.7 billion years ago, new cell types (the forerunners of modern plants) emerged. They were capable of building up (synthetizing) complex nutritious molecules themselves; the energy necessary for these processes was derived from *photosynthesis* (the chemical process that utilizes the energy from rays of light for building up nutrients inside the cells, and consumes CO_2 in the process). When these cells died, the complex molecules they had created dissolved in the surrounding fluid and became accessible as nutrients to the more primitive cells (fig. 2-2B).

The photosynthetic cells absorbed the CO_2 dissolved in the surrounding fluid and kept the absorbed carbon (C) molecules for the photosynthetic synthesis of nutrients; the surplus O_2 was

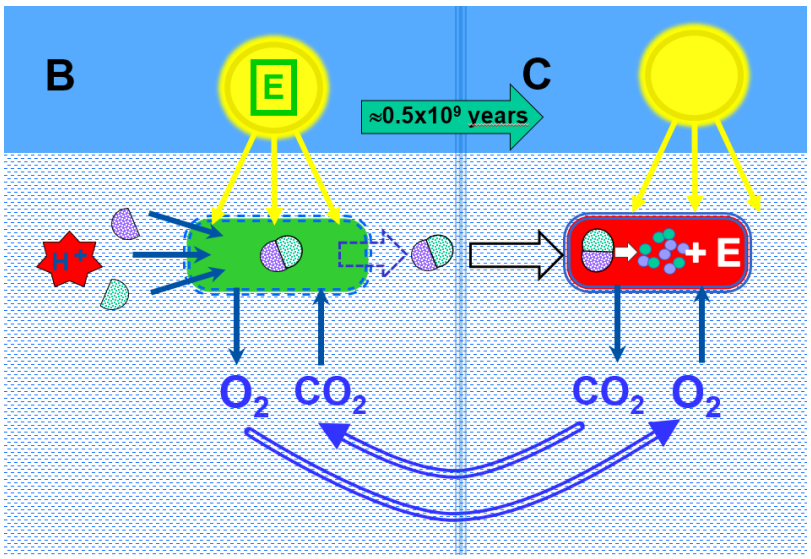

Figure 2-3. *The new aerobic cells* (**panel C**) *could utilize the O_2 generated by photosynthetic cells, and possessed defenses against the toxic effects of O_2. The new metabolic processes released about 20 times the energy as those in the more primitive cells. Their major waste product, CO_2, was re-utilized by the photosyntetic cells* (**panel B**).

discharged as a *waste* product (fig. 2-2B). Accordingly, the quantity of O_2 in the sea and atmosphere began to increase as these cells multiplied. As the amount of iron (as ferrous iron, Fe^{++}) dissolved in the ocean was considerable, most of the excreted O_2 initially reacted with iron to form insoluble iron oxides that settled on the bottom of the ocean. The increase of molecular O_2 in water, and subsequently in the atmosphere, was, therefore, a very slow process; the increase in atmospheric O_2 was modest for almost two billion years, then started to increase substantially about 600 million years ago (fig. 2-1).

Oxygen was, however, toxic to the primitive cells (see oxygen toxicity), as it is to some strains of anaerobic bacteria today. Some of the primitive cell types developed defense systems (scavengers, enzymes (7, 8)) that allowed them to neutralize most of the toxic oxygen species and thus continue functioning also in an O_2-rich environment.

Initiation of aerobic metabolism.

Over two billion years ago, a new type of cell came into being, with enzyme systems that made it possible to utilize molecular O_2 to metabolize nutrients more completely while avoiding most of the toxic effects of oxygen. This resulted in a radical (up to x 20) increase in the energy liberated during the combustion of nutritious substrate molecules.

For this metabolic process to function, the electrons (e^-) liberated during the breakdown of nutrients in the citric acid cycle must be removed (i.e. transferred to other molecules) continuously. While many molecules may act as electron acceptors, the O_2 species created by the transfer of electrons to O_2 molecules by the electron transport chain are unique, as they subsequently combine with the H^+ in the aquatic environment (Part 5-1) to form H_2O. The major waste product of aerobic metabolism was thus non-toxic and became a part of the surrounding fluid. This *aerobic metabolism* increase in energy gave these cells the capacity to carry out more specialized and energy-demanding functions.

Rise of complex, symbiotic cells.

Some of the new, aerobic cells were the forerunners of today's aerobic bacteria. Others entered into a symbiosis (joint existence) with larger variants of primitive, O_2-tolerant anaerobic cells. This created new cell types that consisted of elements from both the older anaerobic and the newer aerobic cells.

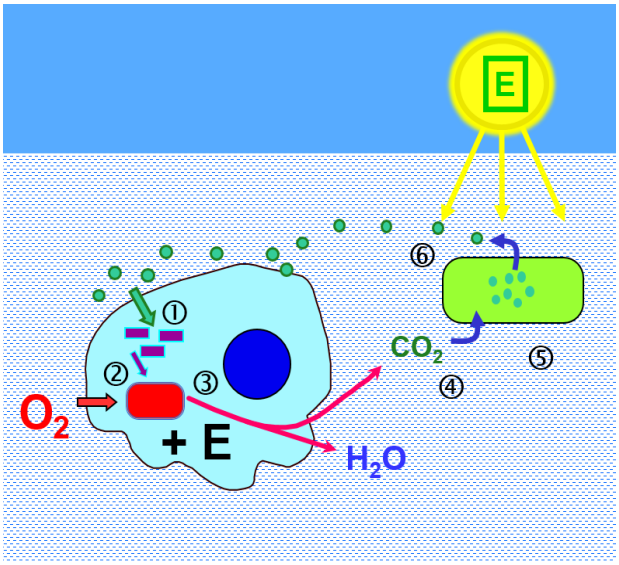

Figure 2-4. *In the complex, symbiotic cells, nutritious substrate entered the cells and were partly degraded in the primitive part ①, further degradation and most of the energy* (**E**) *was produced in the more advanced, aerobic part ②. One of the major waste products, CO_2 ③, was absorbed by photosynthetic cells ④ and utilized as a substrate for their synthesis of new nutritious substances ⑤. Upon death and disintegration of these cells, these nutritious substrates became available to the more complex cells ⑥.*

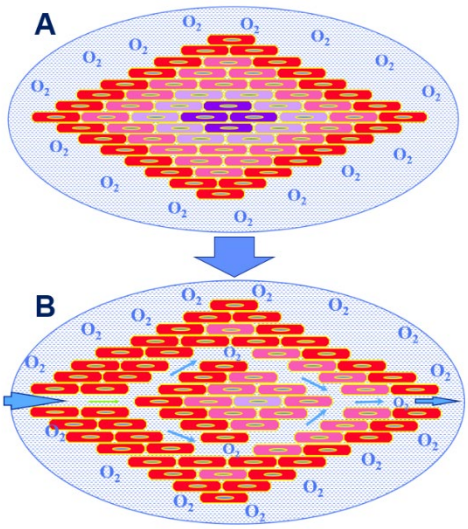

Figure 2-5. *Diffusion distances without* (**A**) *and with* (**B**) *primitive flow-through systems.*

In these symbiotic cells, the initial, anaerobic, breakdown of nutrients took place in the primitive part of the cell. The subsequent O_2-dependent breakdown, liberating the remaining combustion energy with the generation of H_2O and CO_2 as the major end products, took place with the aid of the newer, aerobic element (fig. 2-4), which evolved into mitochondria.

This organization of anaerobic and aerobic metabolism remains, in principle, the same in most of our tissue cells today (see below). This new class of cells had few environmental problems: nutrients and oxygen were present in the water immediately outside the cell membrane, and the excreted CO_2 was absorbed by photosynthetic cells and used as raw materials in *their* production of nutritional molecules (9, 10, 11, 12) (fig. 2-3).

Multicellular organisms.

The first multicellular organisms were probably just aggregates of individual cells. As they grew larger, the diffusion distance for gases and nutrients between the surrounding fluid and the most centrally situated cells increased, limiting their size until primitive systems for convective transport evolved. These were simple channels through an aggregate of cells; when the current increased or the organism moved, oxygen- and substrate-rich fluid would flow through the channels and make more O_2 available to the cells situated farthest from the surface. These systems were the forerunners of the circulatory systems present in all higher organisms today.

The primitive single-cell microorganism's direct access to the surrounding fluid in ponds and oceans has, in our organism, been replaced by the access of tissue cells to the limited supply of nutrients and O_2 gas dissolved in the interstitial fluid. The amounts of these are limited and must continuously be replenished by the blood flowing through the microcirculation (see fig. 2-5 and O_2 requirements below).

The metabolism of human tissue cells.

The co-existence between traits inherited from simpler and more complex cells is still present within the tissue cells in our organism; most of them may be seen as descendants of the early symbiotic cells. In some locations in our organism (e.g. the gut), our tissue cells also co-exist with primitive cells (bacteria, both aerobic and anaerobic), whose number has been estimated to be somewhere between 0.33 and up to 10 times higher than the number of human cells (13)). The number of human cells in the body is vast, and has, in a 70 kg human, been calculated by some investigators (14) to be approximately 3.72×10^{13}, of which a large part are erythrocytes (15). A sophisticated system for the supply of O_2 and nutrients to the interstitial fluid surrounding the tissue cells, as well as for the elimination of metabolic waste products, is necessary for all tissue cells to function normally.

The anaerobic heritage.

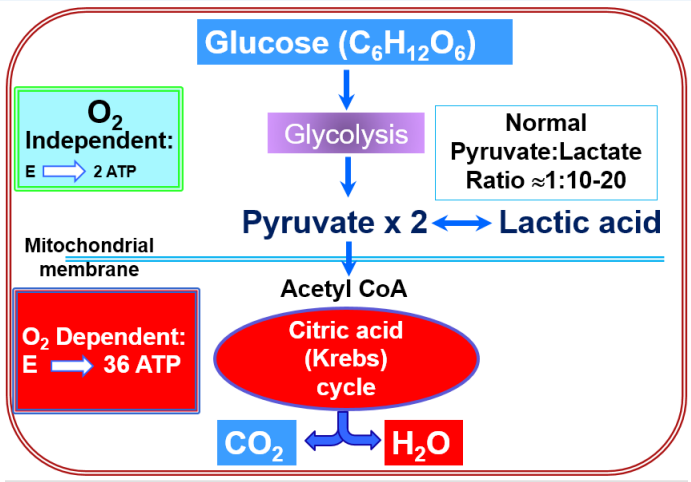

Figure 2-6. *Schematic diagram depicting glucose metabolism and energy* (**E**) *yield (as* ATP*) outside and inside the mitochondrial membrane.*

In the greater part (80-90%) of the volume of our cells (the cytoplasm), initial substrate breakdown occurs through O_2-independent metabolic steps that resemble the biochemical processes of primitive anaerobic cells. This process exploits, however, only a small percentage of the potential metabolic energy of nutrients, e.g. the anaerobic glycolysis of carbohydrates release only about 5% of the latent combustion energy of carbohydrates.

The normal end point of the anaerobic steps in carbohydrate metabolism in human cells is **lactate**. In the presence of sufficient amounts of O_2, its concentration is modest, as most of the molecules from the step before lactate, **pyruvate**, go on to enter the citric acid cycle and are metabolized to CO_2 and H_2O (fig. 2-6). Part of the pyruvate molecules are converted to lactate through the action of the enzyme lactate dehydrogenase (LDH), this reaction is active also under normal conditions but is reversible as long as the citric acid cycle is operative; i.e. the aerobic metabolism is sustained. During normal conditions, the ratio between pyruvate and lactate molecules is around 1:10-20; ratios above this level may signal cellular hypoxia (16) or mitochondrial dysfunction (17).

The aerobic heritage.

The aerobic metabolism takes place in the mitochondria (fig. 2-7), the descendants of primitive aerobic cells. Within these, a chain of enzymes (the *electron transport chain*, also called the respiratory chain, consisting of four complexes, named I to IV) utilize O_2 as an acceptor of electrons (e^-) liberated during a series of stepwise biochemical reactions during the breakdown of nutrients in the *citric acid cycle* or *Krebs cycle*. Simultaneously, **energy-rich chemical compounds** (such as adenine triphosphate, **ATP**) and **waste products like CO_2 molecules** are generated.

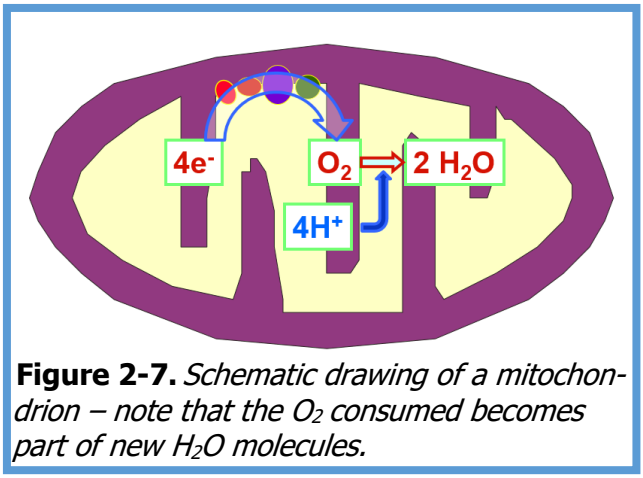

Figure 2-7. *Schematic drawing of a mitochondrion – note that the O_2 consumed becomes part of new H_2O molecules.*

A carbohydrate molecule that is fully metabolized in the citric acid cycle liberates about 20 times more energy than that released by the limited anaerobic metabolism to pyruvate and lactate. The citric acid cycle will, however, slow down or stop if *i)* the concentration of O_2 (see below) becomes too low to absorb the necessary number of electrons, *ii)* the concentration of nutrients are insufficient, *or iii)* the reaction products (e.g. ATP, CO_2) cannot be utilized further *or* carried away by the blood.

The key to the success of the electron transport chain is that the O_2 molecules, which are *reduced* by accepting the (e^-), combine with the free H^+ ions always present in aquatic media to create water (see Part 5-1), i.e. the end product becomes part of their normal environment.

In the absence of functioning aerobic metabolism (mitochondrial dysfunction *or* lack of O_2), increased amounts of pyruvate from glycolysis accumulate and are converted to lactic acid (fig. 2-6). If normal concentrations of O_2 are rapidly re-established, lactic acid is converted back to pyruvate and enters the citric acid cycle where it can be further metabolized. In states with insufficient O_2 supply endures, lactic acid becomes an end product and accumulates within the cells and in its surroundings. The increased lactic acid spills over into the blood, where it is measured as increased lactate (see below)).

The *critical factors* for normal aerobic metabolism are

- **The concentration of O_2 molecules** dissolved in the fluid surrounding the mitochondria (measured as the PO_2 given in kPa *or* mmHg or Torr, see Apx).
- The functional state of the **respiratory (electron transport) chain**.
- The cellular levels of functional **enzymes, co-enzymes,** and **scavengers.**
- The **substrate** availability (i.e. concentration of nutrients inside the cells).

THE OXYGEN REQUIREMENT OF HUMAN TISSUE CELLS

The fluid phase around the tissue cells in the human body is not an almost endless ocean but consists of a thin *film of interstitial fluid* (in adults about 20% of the total fluid quantity of the body, or approximately 12% of total body weight). The reserves of O_2 and nutrients in this film is extremely limited, and must continuously be replenished by the microcirculatory blood. A few seconds without fresh supply of O_2 cause dysfunction of the most sensitive cells like cardiomyocytes and cells in the brain (see also Part 3-3). For normal cell function, the fluid phase surrounding them must therefore receive a continuous supply of more O_2 and nutrients from the circulating blood; at the same time, waste products from cell metabolism must diffuse through the same fluid to be carried away by the microcirculatory blood flow.

Baseline (resting) O_2 consumption ($\dot{V}O_2$) of the body.

At complete rest (i.e. *no activity* of skeletal muscles except those involved in quiet breathing), a 70 kg person of normal build and normal temperature consumes about **250 mlO_2/min**, or approximately 3.5 mlO_2/kg. This value varies, however, with body mass and age (18, 19) and also with the method utilized for measurements (20). As the resting *normal supply of O_2* to the

organism (the global O_2 delivery, **DO_2**) is around 1000-1200 mlO_2/min (see DO_2 below), about 22-25% of the O_2 supplied is extracted (O_2 extraction fraction, **OEF**) from the perfusing blood by the tissues under baseline resting conditions. The DO_2, together with the macro- and microcirculatory flow conditions, determine the delivery of O_2 to the tissues.

The *main task* of the organs participating in the tissue supply of O_2 is to

- Ensure that the O_2 pressure, i.e. the diffusion gradient between the blood in the microcirculation and tissue cells, is sufficient to enable aerobic metabolism in all cells, *and simultaneously*
- Prevent O_2 toxicity by keeping the PO_2 at the lowest levels necessary to ensure a normal S_aO_2, in order to minimize the generation of reactive O_2 species toxic to the cells (see below).

The O_2 consumption of individual organs, *relative* to the O_2 supply (OEF), varies considerably (fig. 2-8), as does the contribution of various organs to the resting O_2 consumption, expressed as the percentage of the total $\dot{V}O_2$ (fig 2-8).

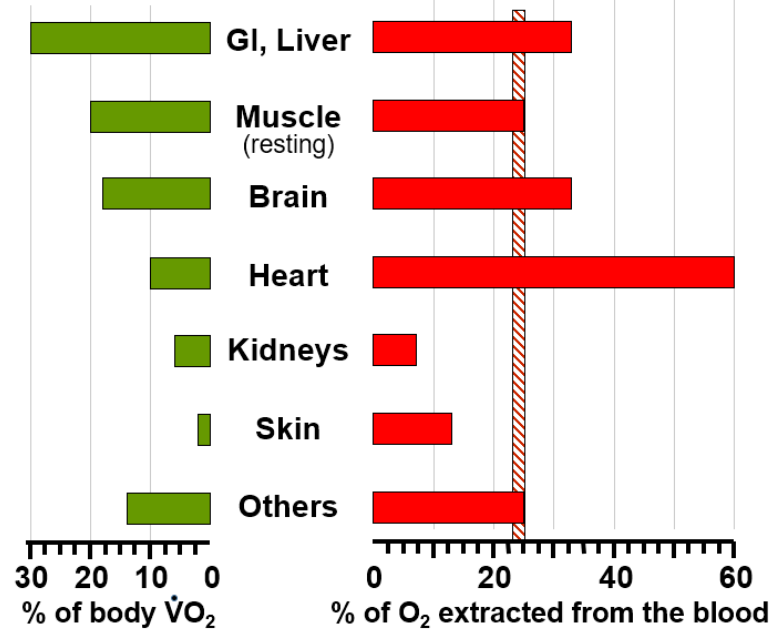

Figure 2-8. Left: *The O_2 consumption of various organs, shown as a percentage of the total body $\dot{V}O_2$.* **Right:** *The O_2 consumption of the same organs, expressed as a percentage of their O_2 supply (the O_2 extraction). The vertical hatched bar indicate the mean O_2 extraction of the whole body.*

At rest, the myocardium of the beating heart extracts almost three times more O_2 from the perfusing blood than the mean of all body organs. Tissues that under normal circumstances have a high extraction ratio are more vulnerable to reductions of the O_2 supply than those with a low ratio. The most vulnerable organs (brain and heart) have, however, the ability to reduce the local vascular resistance (autoregulation) and increase the blood flow (and thus the O_2 supply) when the O_2 demand increases *or* hypoxia threatens.

Pathological changes in metabolism, leading to insufficient intracellular substrate supply *and/or* mitochondrial dysfunction, can lower the $\dot{V}O_2$ (see below). In the text dealing with changes in $\dot{V}O_2$ below, an adequate supply of O_2 and substrate *and* normal mitochondrial function are assumed unless otherwise specified.

Changes in resting $\dot{V}O_2$: effects of temperature, hormones, etc.

Increased resting O_2 consumption. When body temperature increases (*hyperthermia)*, $\dot{V}O_2$ increases by about 7% (21) to 10% (22) per °C. High levels of stress hormones (catecholamines) may increase the $\dot{V}O_2$ by 20-40% (23, 24). In thyrotoxicosis, the $\dot{V}O_2$ may increase by 100% or more (25). In addition, inflammatory (26, 27) and post-exertional states (28) may also increase the resting $\dot{V}O_2$.

Decreased resting O_2 consumption. The most common physiological cause of a major reduction of $\dot{V}O_2$ is *hypothermia*. This principle is utilized by hibernating animals, where a combination of hypothermia and programmed changes in metabolism can reduce the metabolic rate by 75% (in bears (29)) and up to 99% (in smaller animals (30)). Data on the magnitude of the hypothermia effect in non-hibernating organisms varies; in experiments utilizing isolated cells, lowering cell temperature reduces the O_2 consumption by about 10% per 1°C (31), in which case the *ex vivo* $\dot{V}O_2$ will be reduced by 50% when cooling the cells to 30.5°C.

This is in agreement with some (32), but not all (33) measurements in experimental animals and patients during cardiopulmonary bypass. Investigators examining the latter found about 50% reduction of $\dot{V}O_2$ in patients cooled to approximately 24°C, corresponding to a mean 5% reduc-tion per 1°C. The changes in $\dot{V}O_2$ with falling body temperature may not be linear (34); activation of the sympathetic system (catecholamines) and shivering during cooling may increase the met-abolic rate of the organism and interfere with the cooling effects on the cells.

During deep sedation and anesthesia, $\dot{V}O_2$ may decrease by approximately 10-15% (35, 36). Both deep sedation and hypothermia have been used as brain-protective strategy after cardiac arrest (37, 38) and cerebral injury (39). While the former has become standard clinical practice (see also Part 2-4), a beneficial clinical effect of hypothermia on the latter is more uncertain and could not be confirmed by recent investigations (40, 41).

Effect of muscular activity on $\dot{V}O_2$.

Any muscular activity increases the mean $\dot{V}O_2$, and thus the demands on the O_2 delivery (DO_2) system (see below). Ordinary daily activities increase the $\dot{V}O_2$ by about 100-200% from resting values (42, 43); a similar increase often exists during the "at rest" state in investigations of the effect of exercise on the $\dot{V}O_2$ (44, 45). The increase due to muscular activity do not necessarily affect the O_2 consumption of other organs (except for the heart), outside of the general effect of a temperature increase on *all* cells during a heavy workload.

During strenuous exercise, the $\dot{V}O_2$ may increase 10 to 20-fold, depending on the level of fitness (46, 47, 48). When the metabolic rate approaches 20 times resting values in well-trained top athletes, it surpasses the capacity of the circulating blood to sustain a purely aerobic metabolism (i.e. when the rate is above the "lactic acid threshold", ref. 49). Despite the greatly augmented DO_2 under such conditions, almost 90% of the O_2 in the blood may be consumed by the organism (48) (compared to 22-25% at rest). In patients, severe muscular spasms (e.g. epileptic seizures, severe shivering, and generalized convulsions due to cerebral irritation) may have effects com-parable to those found during strenuous exercise (50, 51). During such conditions, the levels of lactic acid in the blood of both athletes and patients may be substantially elevated (see Part 2-4).

Normal tissue levels of O_2 and major waste products.

To maintain a PO_2 sufficient for aerobic metabolism in all cells of a tissue, the blood-to-cell O_2 gradient in the fluid surrounding the cells most distant from the capillaries must be kept above a certain level (see Critical O_2 levels, Part 2-4). The reported **normal tissue PO_2** varies with organs, experimental conditions and methods, approximate values for most tissues lie in the 2.5 kPa to 7 kPa (19 – 53 mmHg) range (52).

Fortunately, the H_2O generated by the aerobic metabolism becomes one with the surrounding fluid, and CO_2 diffuses easily out of the cells, through the surrounding interstitial fluid, and into

the microcirculation (Part 5-2). Under normal conditions, increased metabolism, and thus both O_2 consumption and CO_2 production, are accompanied by increased blood flow which increases the capacity for both O_2 supply and CO_2 removal.

Oxygen toxicity: The Janus profile of aerobic metabolism.

The metabolic benefits derived from the utilization of O_2 as an electron acceptor by our cells come with a price; during each step where an electron is added to the oxygen molecule, reactive intermediates of O_2 are created (fig. 2-9). These intermediates have the potential to damage the cells, analogous to the toxic effect of O_2 on primitive anaerobic cells. The chemical process in which the O_2 molecules accept electrons and combine with H^+ ions to form H_2O occurs in four stages; new reactive oxygen species arise at each stage when additional electrons bind to the O_2 molecule; i.e. the oxygen molecules are progressively *reduced*. Such reactive O_2 species (often called Oxygen Radicals, or more correctly Reactive Oxygen Intermediated, **ROI,** or – Species, **ROS**) are very reactive, they can destroy fats (and thus cell membrane function) as well as proteins and cell DNA and may damage the tissue cells.

During the normal metabolism of O_2 in tissue cells, the electron transfer and formation of H_2O within the mitochondria take place so rapidly that only about 1-2% of the ROS molecules generated diffuse away from the electron transport chain and into the surroundings. The organism has several enzyme systems (e.g. superoxide dismutase, catalase) and ROS-binding molecules (ROS scavengers) that rapidly neutralize ROS (53, 54, 55) and prevent these from damaging enzymes and cell structures. If ROS production increases beyond the neutralizing capacity of these systems (i.e. during dysfunction of the electron transport chain), or the level of protective substances is particularly low, cell and tissue damage will occur (56).

Periods of severe hypoxia can damage the enzymes of the respiratory chain. When oxygen once more becomes available, an increased quantity of ROS is generated and diffuse into the surrounding cellular structures (see Part 2-4, reperfusion injury). An *excess of O_2* in the blood following (e.g. using a F_iO_2 that results in a P_aO_2 higher than that necessary to keep S_aO_2 in the 92-95% range) during the initial period *after* the termination of an anoxic/hypoxic episode may thus have detrimental effects (57, 58, 59).

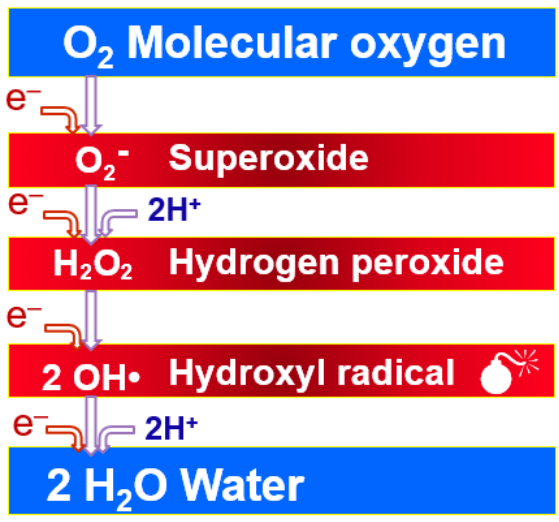

Figure 2-9. *Conversion of O_2 molecules to H_2O occurs as a result of stepwise addition of electrons (e^-) and H^+ ions. All intermediate products are strongly reactive, with OH• being the most toxic.*

Oxygen toxicity in the organism may also occur *without* prior hypoxic damage when the oxygen pressure in the lungs or blood is much higher than normal. Small laboratory rodents (rats, mice, hamsters) that breathe 100% O_2 at normal atmospheric pressure usually develop fatal lung failure with pulmonary edema within three to five days (60, 61). In humans, the continuous inspiration of 100% O_2 for many hours causes a feeling of soreness in the chest and a low-grade inflammatory reaction in the mucous membranes of the respiratory tract (62), and inflammatory markers can be

detected in the larger airways (63). In addition, breathing gas with a high O_2 concentration can cause atelectasis in poorly ventilated parts of the lungs; the use of 100% O_2 as an inspiratory gas for extended periods should therefore be avoided whenever possible (see Part 4-4 for exceptions to this recommendation).

A special type of oxygen toxicity may be seen in the newborn (most frequently in premature babies), where high oxygen pressure in the blood is associated with eye damage (retrolental fibroplasia) (64, 65). These toxic effects are presumably due to the fact that the increased quantity of O_2 molecules raises the production of ROS so much that the neutralizing agents (enzymes and scavengers) are overcome. Inspiration of 100% O_2 at increased barometric pressure (from about two atmospheres and higher, during diving or in hyperbaric chambers) may affect the brain cells and cause unconsciousness and convulsions (66) in healthy adults.

Some of the body's leukocytes (granulocytes, monocytes, and macrophages) contain high concentrations of a specialized enzyme (NADPH oxidase) that enable them to produce large quantities of ROS. The evolutionary purpose of this production is to use ROS to kill microorganisms (67, 68). Such cells can also be activated by various types of pro-inflammatory stimuli *without* the presence of microorganisms (e.g. signal molecules generated by any kind of tissue injury), they can then attack and damage the body's tissues (69, 70) as part of an acute inflammatory response (see also Part 4-3, ARDS).

Certain drugs used in cancer treatment (e.g. the cell toxin bleomycin) have been associated with a marked increase in oxygen toxicity in the lungs, so that even a moderate increase in the F_iO_2 may cause increased lung damage. The danger of a short-term increase in F_iO_2 is probably modest (71); the role of high oxygen concentrations in this type of toxicity is not clear-cut, as these types of drugs can have toxic effects on the lungs also when breathing air with *normal* oxygen pressures.

2-2. MICROCIRCULATION: THE AEROBIC LIFELINE OF THE CELLS

The supply of O_2 and nutrients *to* the tissues, plus the removal of CO_2 and other metabolic waste products *from* the tissues, are dependent on the flow of blood through the microcirculation. Of these, the O_2 supply is the most crucial factor, as anoxia may lead to loss of cellular function within seconds (Part 2-4). A substantial accumulation of CO_2 may, on the other hand, be well tolerated if hypoxemia is avoided (see Part 4-4).

The microcirculation and O_2 supply to tissue cells.

The microcirculation consists of *small precapillary vessels*, *capillaries*, and *small post-capillary venules*. Most of the exchange of gases, nutrients, and waste products between blood and tissue takes place in the capillaries; thin-walled pre- and post-capillary vessels also participate in this exchange to a limited extent (see the modified Krogh's cylinder below). The capillary wall represents little obstacle to gas diffusion, the PO_2 in a thin film of interstitial fluid closest to the outside of the capillary is only marginally lower than that in the microcirculatory plasma.

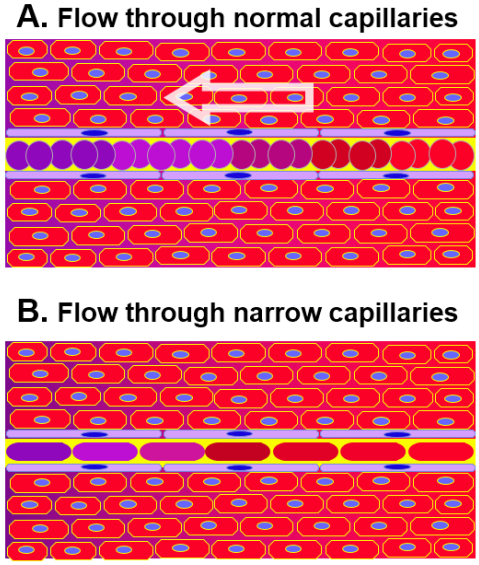

Figure 2-10. *When flowing through wide capillaries* (**A**)*, the erythrocytes have a spherical shape. When entering capillaries with a diameter smaller than their normal diameter* (**B**)*, normal erythrocytes adapt their shape to their environment.*

Some capillaries have a diameter smaller than the normal erythrocyte diameter. The Hb molecule suspension inside the erythrocytes behave as a viscous fluid; although erythrocytes commonly are depicted as circular, biconcave discs, the cell membrane of normal erythrocytes is easily deformable (72). In the microcirculation, the erythrocytes function like miniature droplets of fluid in which Hb molecules are suspended, enclosed by a thin film. This facilitates their passage through narrow capillaries (fig. 2-10). Increased erythrocyte stiffness (e.g. after storage, sickle cell disease – see below) may, however, impede their passage through the smallest capillaries. The diffusion distances between Hb molecules suspended within normal erythrocytes and the tissue are not much different from what would be the case if the Hb molecules were suspended in the plasma; the O_2-transporting properties of Hb molecules change, however, drastically in the environment outside the erythrocytes (see Part 2-3 Hemoglobin below).

From a tissue cell's point of view, the main task of the microcirculation is to supply blood at a flow rate and with an O_2 content sufficient to keep the PO_2 gradient between the microcirculatory plasma and tissue cells high enough to satisfy the O_2 demands of the mitochondria. The PO_2 in the systemic capillaries (P_cO_2) should therefore be high enough to ensure that all tissue cells, also those situated farthest from the arterial end of a capillary, can maintain an aerobic metabolism (fig. 2- 11).

On the other hand, an excess of O_2 above this level increases the risk of toxic effects from ROS generation (see O_2 toxicity above). Hyperoxia is also associated with a reduction of total organ flow (cardiac output) and an increase in systemic vascular resistance (73), both of which may reduce microcirculatory flow. An arterial, and thus capillary, PO_2 considerably above normal

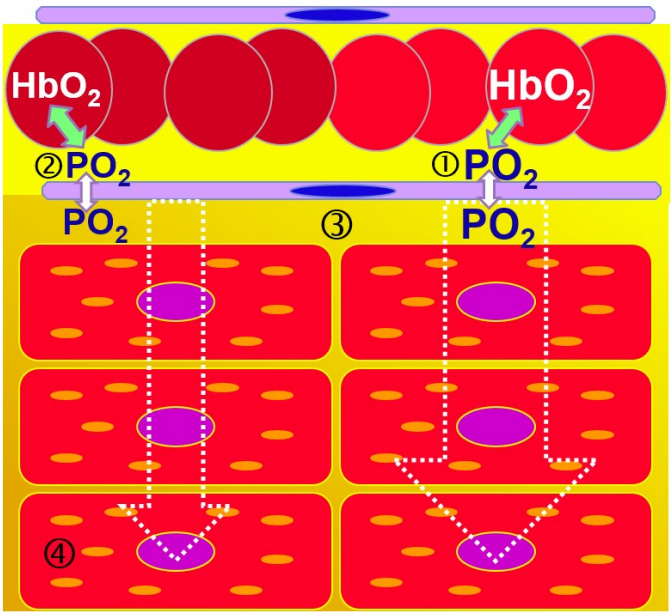

Figure 2-11. *The microcirculatory PO_2 is determined by the HbO_2 saturation and the Hb affinity for O_2. As O_2 continuously diffuse out of the vessels, the PO_2 at the arterial end ① is higher than at the venous end ②. PO_2 in the interstitial fluid close to the capillary wall is close to that of the blood ③, but decreases with distance from the vessels and the number of other O_2-consuming cells between each individual cell and the capillary ④.*

should, as a general rule, be avoided; there are, however, important exceptions (e.g. carbon monoxide intoxications, severe acute anemia, air embolism – see also Part 4-4).

In addition to supplying suitable amounts of O_2, the blood flow through the microcirculation must also be able to supply sufficient amounts of nutritious substances. Simultaneously, it must also allow for elimination of the waste products at the same rate as their generation, to avoid pericellular accumulation and thus a reduction in metabolic rate (see Part 2-1).

The Krogh's cylinder: the classical and the modified concept.

The capillary circulation is often portrayed as multi-layered tubes of tissue cells with the supplying capillary in a central position (Krogh's cylinder (74), see fig. 2-12)). The supply of O_2 and nutrients (arrows) is determined by their concentration in arterial blood *and* the flow rate through the capillaries; their concentration is always highest at the arterial end of the capillary. As the O_2 diffuses continuously from blood to tissue, the capillary PO_2 decreases towards the venous end. The opposite is true for metabolic waste products and CO_2. Under normal conditions, the cardiac output, and thus also the capillary flow, adjusts to increased O_2 demands so that the concentration of nutrients and O_2 remains high enough to supply even the most peripherally situated cells at the venous end with amounts adequate for sustaining aerobic metabolism.

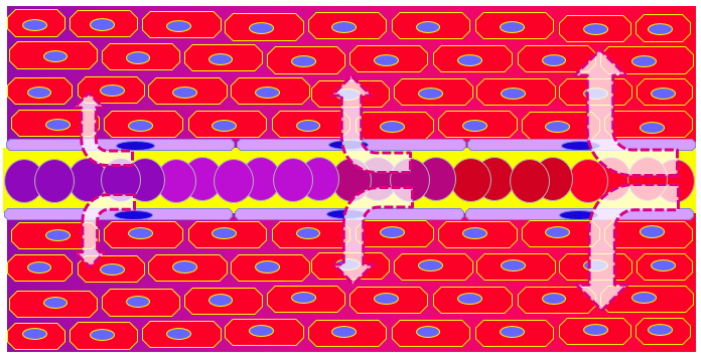

Figure 2-12. *Krogh's cylinder. Decreasing size of arrows symbolize falling concentrations of O_2 and nutrients, and their gradients, towards the venous end of the capillary.*

The Krogh's cylinder illustrates fundamental aspects of the dynamics of gas and soluble molecule diffusion in tissues. It is an idealized model, as all capillaries in a tissue rarely run parallel to each other and with blood flow in the same direction but often cross each other in any direction. Where thin-walled pre-capillary and post-capillary vessels run close to, or cross, another, diffusion of gas, fluid, and other substances may occur directly from vessel to vessel (75, 76, 77) (fig. 2-13).

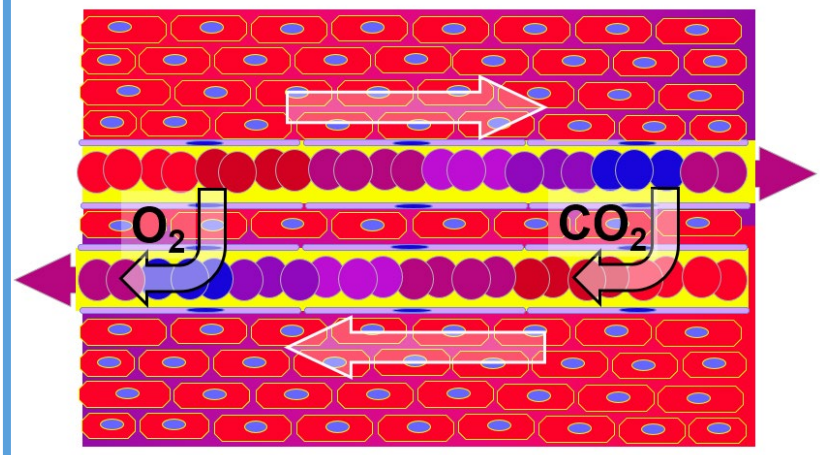

Figure 2-13. *Krogh's cylinder modified. Where precapillary arterioles and postcapillary venules pass each other, O_2 may diffuse from arterioles to venules while CO_2 diffuses in the opposite direction.*

Some CO_2 may also diffuse from the venous end of the microvessels into pre-capillary vessels, increasing the H^+ concentration and thus decreasing the HbO_2 affinity *before* the blood enters the true capillaries. When this happens, the capillary blood can release more O_2 to the tissues before the PO_2 decreases to critical levels (see effect of acidosis on the HbO_2 dissociation curve, fig. 2-20). As O_2 may diffuse from pre-capillary to post-capillary vessels (fig. 2-13), another consequence is that the venous blood draining the tissues has a higher PO_2 and a lower PCO_2 than those in the interstitial fluid surrounding the tissue cells. This pre- and post-capillary gas exchange may explain why the content of O_2 in the veins draining a tissue can be higher than that measured in the tissue surrounding the vessels.

The structure of the microcirculation varies considerably between different tissues; the metabolic rate of the tissue seems to be an important factor in the pattern of local O_2 delivery. As the transport of O_2 from the plasma phase of the blood to the cells most distant from the arterial end of the capillary mostly depend on gas diffusion, the magnitude of the **blood-to-cell PO_2 gradient** determines whether or not aerobic metabolism is possible for all cells.

Regardless of how the vessels of the microcirculation in a particular tissue are organized, the higher the blood-to-cell O_2 gradient, the higher the capacity for O_2 diffusion from blood to tissue. The gradient depends mainly on

- The **PO_2 in the arterial blood,** and the **capacity** of the **Hb** to release enough O_2 to uphold the **plasma PO_2** above critical levels during the passage through the capillaries (see O_2 content of the blood (C_aO_2) below),
- The **flow rate** of this blood through the microcirculation.

Release of O_2 from plasma in the microcirculatory blood.

The **amount of O_2** dissolved in the blood (i.e. the number of O_2 molecules not bound to Hb at a PO_2 of 13.3 kPa (100 mmHg)) when it enters the arterial end of the capillaries constitutes only about 6% of the total amount of O_2 needed by the tissues of a resting organism. The amount of O_2 carried by each gram of Hb, if fully saturated with O_2, is, however, about 4.5 times higher than that dissolved in arterial blood (see calculation examples below). As the O_2 molecules diffuse out of the capillaries and the plasma PO_2 decreases, more O_2 molecules are released from Hb to replenish those consumed by the tissue cells. This keeps the capillary PO_2, and thus the blood-to-cell gradient, above critical levels (see Part 2-4). At an Hb of 15 g/dl, each 1% decrease in SO_2 releases an amount of O_2 from their binding to Hb comparable to about 67% of the total amount of dissolved O_2 in arterial blood at normal P_aO_2.

Determinants of systemic microcirculatory flow.

The microvascular **flow rate** is determined by

- **The perfusion pressure** or **forward pressure** of the blood; i.e. the difference between the hydrostatic pressure of blood before and after its passage through the tissue. In most organs (except for the liver and pituitary gland), the perfusion pressure is the same as arterial blood pressure *minus* the pressure in the veins that drain the organ. The hydrostatic pressure in the microcirculatory vessels is, however, much lower than the perfusion pressure, as most of the systemic vascular resistance is situated in the small arterioles upstream to the microcirculation (see below). Venous pressure varies from organ to organ but must always be higher than the mean central venous pressure.
- **The vascular resistance** of the vessels perfusing the organ. This depends on the *dimensions of the vessels*, primarily the arterioles, which are partly determined by the balance between the vessels' endogenous contraction and dilatation (e.g. sympathetic stimulation, release of nitrogen monoxide). In addition, the *pressure of the tissue surrounding the vessels* inside the organ affects the transmural pressure and therefore vessel dimensions. Extremely high tissue pressures (e.g. cerebral edema, post-hypoxic or post-traumatic edema in muscle compartments, high intraabdominal pressures) may obstruct the circulation more or less completely and produce ischemic tissue damage. Any *local obstruction of the vessels* (thrombosis, stenosis) also increases vascular resistance.
- **The viscosity of the blood** normally depends on the number of red blood cells (usually measured as hematocrit (Hct) or Hb) and their rigidity (see also transfused erythrocytes and sickle cells below). In disease, substantial changes in the number of thrombocytes, leukocytes (mostly in leukemia), and protein content of the blood (mostly in hyper-gammaglobulinemia) may also influence the viscosity (78).

The correlation between blood flow through an organ (**Q**), the perfusion pressure (**P**), and the resistance to blood flow (**R**) may be expressed by the equation

$$\mathbf{R} = \frac{\mathbf{P}}{\mathbf{Q}} \quad \text{or as} \quad \mathbf{Q} = \frac{\mathbf{P}}{\mathbf{R}}$$

where **R** includes both vascular and viscosity effects. The equation illustrates that if the *perfusion pressure* decreases, the blood flow can be maintained if the resistance decreases by the same fraction (as in cerebral and cardiac autoregulation). If the *resistance* increases, the perfusion pressure must increase to the same degree to maintain unchanged flow (see also Part 3-1 and Apx).

FLUID EXCHANGE IN THE MICROCIRCULATION, EDEMA

The capillary wall consists of the basement membrane, the endothelial layer, and the glycocalyx covering the luminal side of the endothelium (fig. 2-14). These layers are readily permeable to gases, fluid and nutrients of low molecular weight (such as glucose); the permeability to larger molecules (e.g. albumin, globulins) is low (see also Apx, oncotic pressure). Shifts in the balance of fluid between the *plasma water inside* the capillary bed and the *interstitial fluid* in the space on the *outside* is normally regulated by two opposing forces:

- The **hydrostatic pressure gradient**, which forces fluid *out* of the capillary,
- The **colloid osmotic pressure gradient** which may draw fluid back **into** the capillary.

The balance is also affected by the capillary wall's permeability to water and molecules, this is characterized by a constant (K). Under normal conditions, this constant varies between different

types of capillary beds; acute inflammatory states may change the permeability for both fluid and protein molecules dramatically (see inflammation below).

The **effective hydrostatic pressure** (the *transmural* hydrostatic pressure) that forces fluid out of the microcirculatory capillaries is the difference between the pressure of blood inside the vessel and the pressure of the interstitial fluid on the outside. At normal pressure conditions, the balance favors flow of fluid out of the capillaries; subnormal capillary pressures (as in hypovolemia) favor fluid resorption.

The **effective colloid osmotic pressure** (the *transmural* colloid osmotic pressure) opposes the hydrostatic pressure and may draw fluid into the vessel when the hydrostatic pressure is low. It is made up of the difference between the concentration of molecules with colloid osmotic effect (primarily albumin) in the blood and the interstitial fluid outside.

Fluid balance, according to the concept of Starling: classical and revised.

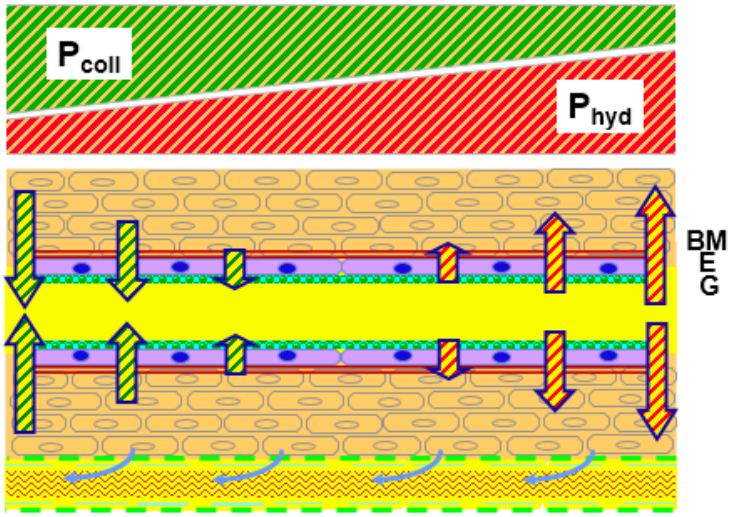

Figure 2-14. *The classical Starling concept: Hydrostatic pressures* **(P_{hyd})** *force fluid out of the capillaries at the arterial end, and colloid osmotic forces* **(P_{coll})** *induce reabsorption at the venous end. A net difference, drained by the lymphatics, results from either increased hydrostatic- or low colloid pressures.*
BM: *Basement membrane,* **E**: *Endothelial layer,* **G**: *Glycocalyx.*

In the microcirculation, the **classical concept** was that there always is some filtration of fluid from blood to interstitium at the arterial end of the capillary and that most of the fluid was reabsorption at the venous end (fig. 2-14). This concept, first described by Starling (79) and for many years generally accepted by most of the medical community, has been challenged by several investigators (80, 81, 82).

The newer concept, the **Revised Starling equation**, focuses on the importance of the glycocalyx, and that the volume of reabsorbed fluid under normal conditions is small compared to the amount filtrated out (fig. 2-15). The volume of fluid reaching the lymphatic vessels of the tissues before being transported back to the blood is larger than assumed previously and has been estimated to be approximately 8 liters/24 hours (80). On the other hand, under conditions with very low microcirculatory hydrostatic pressures (e.g. hemorrhagic hypotension, acute vasodilation) as much as 500 ml can be reabsorbed into the microcirculation from the interstitial fluid within 15-30 min (80).

An increased transcapillary flow increases the convective capacity for gas and nutrient supply to the tissues. Increased extravasation of fluid can be dealt with as long as the total quantity of fluid does not exceed the transport capacity of the lymphatic system; if an imbalance occurs, interstitial edema arises (see below).

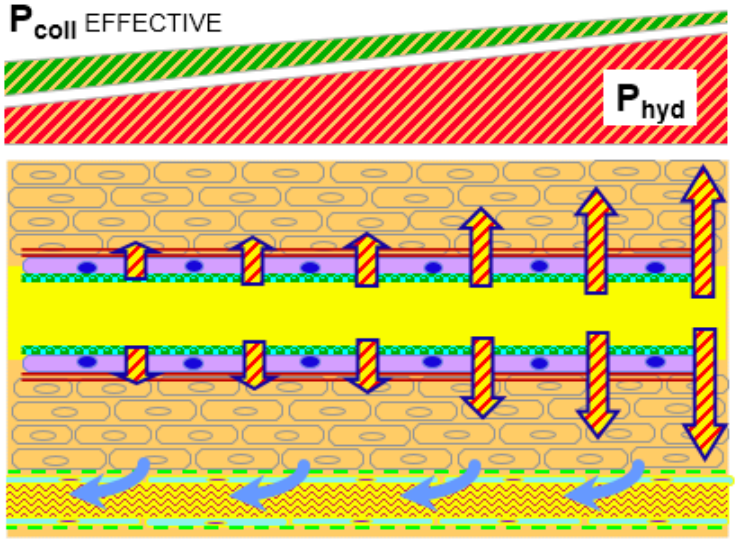

Figure 2-15. *The revised Starling concept, in which the hydrostatic pressures under normal conditions are always higher than the colloid osmotic pressures at the whole length of the capillary. The filtered fluid must be removed by the lymphatic vessels.*

The structure and normal permeability of the endothelium varies from organ to organ (83), and the structure and thickness of the glycocalyx also vary between different organ systems (84.) and determine how readily fluid and colloids pass through the vessel wall. The extremes are on one hand the microcirculation of the liver, which is almost totally permeable to both fluid and large molecules, on the other, the microcirculation of the brain, in which the capillary walls are extremely dense, constituting the so-called blood-brain barrier.

Tissue edema formation.

Edema occurs when the net flow of fluid from the microcirculation becomes greater than the capacity of the lymphatic system to transport the fluid back to the blood. Such an imbalance may arise through three different mechanisms:

- **Increased hydrostatic pressure in the capillaries** (hydrostatic edema)
- **Increased permeability of capillary wall** (permeability edema, capillary leakage).
- **Decreased oncotic pressure in the blood** (most often low blood albumin)

Factors that impede the lymph transport (increased pressures in tissue surrounding the vessels, mechanical damage, and gel formation due to activation of extravasated proteins of the coagulation cascade) also increase the tendency to edema formation.

Hydrostatic edema may occur in the absence of any disease state (e.g. edema in the legs when standing still for long periods). Otherwise, such visible edema is often seen in heart failure (actually **right ventricle failure,** see Part 3-3), where the increased venous pressure created by right ventricular failure and/or diastolic dysfunction is transmitted backwards to the capillaries and increases fluid extravasation. As edema fluid begins to accumulate in the interstitial space, it creates an increasing counter-pressure to the blood pressure inside the capillaries. The transmural hydrostatic pressure decreases; the filtration of fluid out of the capillaries declines with increasing edema formation. In loose tissues, however, large amounts of edema fluid may accumulate before the interstitial hydrostatic pressure increase substantially (85).

It is uncertain whether **low albumin content** in the blood *alone* generates edema, but extremely low albumin levels cause formation of edema at lower levels of hydrostatic transmural pressure. Patients with chronic liver damage (cirrhosis) often have a tendency to edema formation in the abdominal cavity (ascites) and the legs due to high hydrostatic pressure in the microcirculation of the bowel and mesentery combined with low albumin levels. The *effective* albumin concentration gradient between capillaries and interstitial fluid may be smaller than previously assumed (80). The percentage of albumin in the interstitial fluid relative to blood also varies with experimental models, species, and measurement methods; values between 21% and

63% have been reported (86). The permeability of the microcirculation also differs between types of tissue; in a study of human volunteers, the ratio between the albumin concentration in human interstitial fluid and blood was found to be approximately 27% in muscle, while that in adipose tissue was 15% (80).

Increased vascular permeability as a result of anaphylactic reactions may occur within seconds to minutes, *or* develop gradually after the release of pro-inflammatory agents after infections or tissue damage. The endothelial cells contain small quantities of contractile elements (actin-myosin) that resemble those in muscle fibers. In the event of strong stimulation (e.g. *anaphylactic reactions* with the release of histamine or other substances), the endothelial cells may contract so powerfully that open space arises between them (see Inflammatory changes below). Dysfunction of the complement system, often due to lacking inhibition of the complement C1 factor (87, 88) and involving activation of other cascade systems (89), may in rare instances create acute microvascular leakage and edema (angioedema). Both fluids and proteins leak out rapidly; as vasodilation also occurs simultaneously, the combination of fluid loss and dilated vessels reduces the venous return and cardiac filling pressures, and the intravascular compartment becomes "hypovolemic" within minutes (see Part 3-3). In animal experiments, a capillary permeability 25 times normal was seen when an anaphylactic reaction was induced by i.v. infusion of an allergen (90).

The most common cause of acute or subacute increased vascular permeability in the microcirculation is, however, *inflammatory processes in the tissues.* Such processes may be localized within limited tissue areas, but may also be generally disseminated within an organ or throughout the whole body. The condition in which a generalized inflammatory process affects the body as a whole is often referred to as **SIRS** (Systemic Inflammatory Response Syndrome, see ref. 91). This syndrome is often accompanied by general vasodilation and low peripheral vascular resistance (92) (see also Part 3-3); if caused by microorganisms in the blood (sepsis), cardiac dysfunction may aggravate the extravasation of fluid by increasing the mean venous, and thus also the microcirculatory pressures.

Unlike hydrostatic edema, edema due to capillary leakage does not necessarily occur where the hydrostatic pressure is highest, but where the inflammatory process is most pronounced and the blood flow is best maintained. Since inflammation increases permeability of vessels to albumin as well as water, the difference in intravascular and extravascular colloid osmotic pressure is reduced and will be of less significance in this type of edema. On the other hand, increased hydrostatic pressure in the capillaries will enhance edema formation also in capillary leakage edema; this constitutes an indication for keeping the venous pressures as low as possible without compromising the cardiac preload (see Part 3-1) in such patients.

2-3. HEMOGLOBIN AND OXYGEN TRANSPORT

THE HEMOGLOBIN (Hb) MOLECULE: PROPERTIES AND BINDING OF O_2

The hemoglobin (**Hb**) molecule is a protein with a molecular weight of approximately 64 500 Da; it consists of four separate subunits, the **monomers** (fig. 2-16). These are not identical but have a similar size and molecular weight. In clinical medicine, the Hb concentration in the blood is usually given in either **g/dl** or **g/l**; the use of the more logically correct unit **mmole** (see Apx) is largely restricted to scientific publications. A source of confusion when the Hb concentration is given in mmol/l is that some researchers use the molecular weight of the whole molecule, the *tetramer*, as the molecular weight base while others use the weight of the *monomer*. A benefit of using the monomer concentration as the base is that if all monomers are saturated with O_2, the concentration of Hb monomers and Hb-bound O_2 molecules will be the same if both are given in mmol/l. A comparison of values given in grams and moles (based on the tetramer and monomers) is shown in table 2-1.

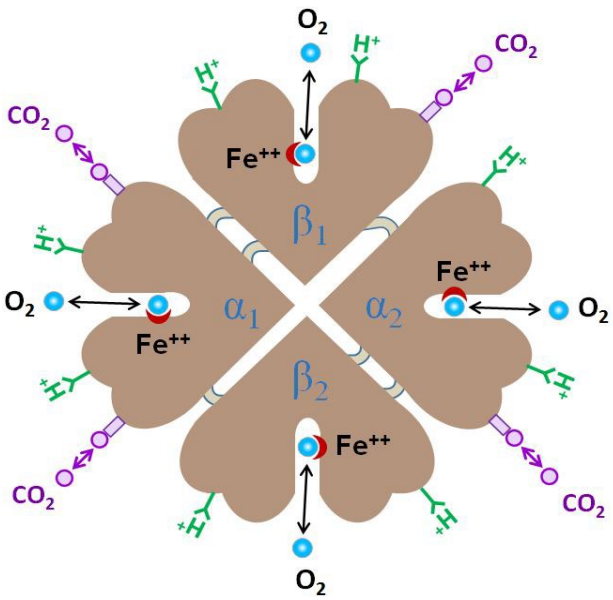

Figure 2-16. *Graphic presentation of the hemoglobin molecule; the whole molecule (the tetramer) consists of four globins (2 α and 2 β monomers) bound together by the chemical attraction between various parts of the globin structure. The binding of CO_2, H^+ and 2,3 DPG changes molecule function, but occurs at locations different from the O_2 binding site.*

The erythrocytes, with the Hb molecules suspended inside, are like wagons of an endless freight train running on a circular track, loading and unloading O_2 without stopping and transporting the bulk of the O_2 necessary for aerobic metabolism from the alveolar gas to the tissue cells. On the return trip, they carry part of the CO_2 generated by the tissue as *carbamino compounds* to the lungs for excretion. The unique properties of the Hb molecule are what make aerobic metabolism of the human organism possible (see calculations below); structural or functional changes that abolish its role as a reversible O_2 carrier are incompatible with life.

The molecular structure of normal hemoglobin.

The four heme-containing globins are coupled to each other by strong chemical bonds. These chemical bonds act also as a signal system; a change in the chemical configuration of one monomer also affects the configuration, and thus the function, of the others. Embedded in each globin is a heme group containing a bivalent iron molecule (ferrous iron, Fe^{++}) that can bind one O_2 molecule reversibly. The whole Hb molecule (the *tetramer*) thus can bind four O_2 molecules (fig. 2-16).

The globins consist of amino acid chains convoluted into a three-dimensional structure; the heme group is not situated on the surface, but in a cleft of its molecular structure. The affinity of each

Hb values and units.			
g/dl	g/l	mmol/l (A)	mmol/l (B)
Conventional	Conventional, *SI accepted*	Tetramer, *CF: 0.1551.*	Monomer, *CF: 0.6206.*
1	10	0,155	0,621
2	20	0,310	1,241
3	30	0,465	1,862
4	40	0,620	2,482
5	50	0,776	3,103
6	60	0,931	3,724
7	70	1,086	4,344
8	80	1,241	4,965
9	90	1,396	5,585
10	100	1,551	6,206
11	110	1,706	6,827
12	120	1,861	7,447
13	130	2,016	8,068
14	140	2,171	8,688
15	150	2,327	9,309
16	160	2,482	9,930
17	170	2,637	10,550
18	180	2,792	11,171
19	190	2,947	11,791
20	200	3,102	12,412

Table 2-1. *Units used to give Hb concentration (see text); conversion factors (CF), relative to concentrations in g/dl, is shown on top. Green indicate normal range, lilac the range that is accepted by most of the medical community for many seriously ill, but circulatory stable, patients.*

monomer's heme group for O_2 varies with both changes in the chemical bonds *within* the monomer, and with changes in the three-dimensional structure of the whole Hb molecule. A variety of factors can induce HbO_2 affinity changes, i.e. a change in the way Hb binds and releases O_2 also changes the equilibrium between PO_2 and SO_2 in the blood. In addition, some gases and chemicals may induce changes that render the Hb molecule unable to function as a transporter of O_2. An overview of the more important factors affecting the binding of O_2 by Hb molecules is given below.

Hb binding of O_2 and O_2 saturation (SO_2).

When all four binding sites are occupied by O_2, the Hb molecule is *saturated* with O_2. For each single Hb molecule, the binding can be envisioned as an all- or nothing state, as the binding of an O_2 molecule to *one* monomer immediately leads to the binding of O_2 molecules to the remaining monomers, and *vice versa.* There are, however, intermediate states, which probably exist for only a very limited time due to the co-operativity of the monomers (93).

Whether or not a normal Hb molecule is saturated with O_2 depends primarily on *the concentration of O_2 molecules in the surrounding fluid* (fig. 2-17). The binding of O_2 is modified by changes in the Hb molecule's *affinity* for O_2 (see HbO_2 dissociation curve below) and by the presence of *other molecules* (e.g. carbon monoxide, CO) which compete with the O_2 molecules for binding to the same binding site *or* interfere with O_2 binding in other ways. The state of an Hb molecule is often described as either *oxygenated* ("relaxed") or *deoxygenated* ("tense") (fig 2-17). In the deoxygenated, "tense" (**T**), state, the access of O_2 molecules to the Fe^{++} binding sites is partially obstructed and the affinity for O_2 is low (corresponding to a rightward shift of

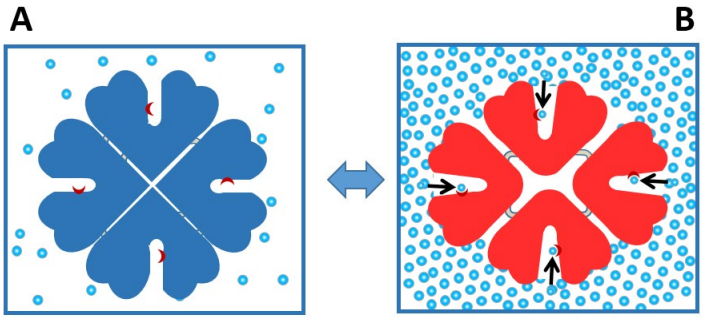

Figure 2-17. *Hb molecule in the deoxygenated, **tense state** **(A)** and the **oxygenated, relaxed state** **(B)**. The density of the O_2 molecules surrounding the Hb determines the probability of a given Hb molecule to be in ether state.*

the HbO_2 dissociation curve, see below). The ability of Hb molecules to bind CO_2 as carbamino groups (see also transport of CO_2 below) is also greatly increased when the molecule is in a deoxygenated state. Hb molecules that have released their O_2 in the microcirculation thus increase their ability to transport CO_2 to the lungs (the *Haldane* effect). In the oxygenated, "relaxed" (**R**), state, access is easier and the affinity of the Hb molecules for O_2 is high (corresponding to a leftward shift of the HbO_2 curve) and CO_2 bound as carbamino groups is easier released.

The HbO_2 saturation, usually reported as SO_2, is the mean number of O_2-saturated Hb molecules in an erythrocyte or a blood sample, relative to all Hb molecules present (fig. 2-18). Blood in which the hemoglobin has a high SO_2 is bright red, while blood with a lower SO_2 (partly or fully deoxygenated) is a dark bluish lilac. When the microcirculation is filled with such blood, the skin and mucous membranes of the patient become cyanotic. The mass of desaturated Hb determines whether or not cyanosis becomes apparent, a content of desaturated blood higher than approximately 5 g/dl is assumed to be necessary for the clinical detection of cyanosis (94). In patients with a high Hb content in the blood, cyanosis is visible even at a modest degree of desaturation (S_aO_2 90% if the Hb is 15 g/dl (95)). Patients suffering from severe anemia (Hb < 5-6 g/dl) may show no clinical cyanosis even if the S_aO_2 is extremely low. Arterial blood samples from hypoxemic patients with severe anemia also look brighter red than expected from a low saturation state of the arterial blood.

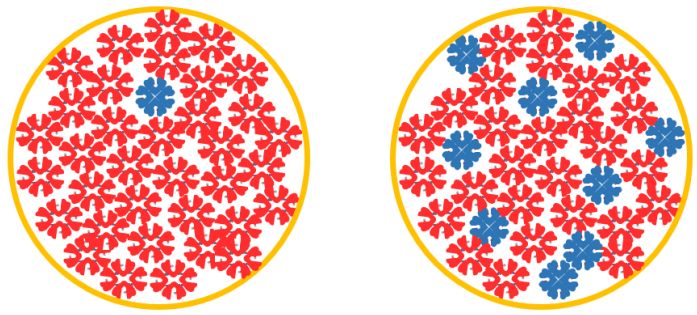

Figure 2-18. *Schematic drawing of erythrocytes where 97.5% or 75% of the Hb molecules are saturated with O_2.* **Left** *SO_2 = 97.5%, normal arterial saturation,* **Right** *SO_2 =75%, normal venous saturation.*

Normal variations in hemoglobin structure.

A wide variety of monomers, and thus also of Hb tetramers, exists. The most common Hb type in adults in the western world, **HbA**, consists of two *alfa* (α_1 and α_2) - and two *beta* (β_1 and β_2) *globins*. During gestation and the first weeks after birth, the major Hb type is the fetal variant of Hb, **HbF** (96). At full-term birth, the baby's blood still contains around 80% HbF. The HbF molecules lack β globins; instead, they have another type of globin subunits, *gamma* (γ) *globin* in place of the beta globins. The production of these γ globin chains starts to decline about 30 weeks after conception and becomes insignificant after about 50 weeks. During this interval, production of β chains commences; at 50 weeks, β chain production has largely replaced that of γ chains. Due to the long life span of erythrocytes, HbF still represents a substantial part of the total mass of Hb molecules (75-85%) at the end of normal pregnancy (97). There remains, however, a low-level production of HbF (between 0.3 and 4.4% of the total Hb) also in most adults (98).

Many other Hb types exist (see variant Hbs below), the incidence of some of them is more prevalent in certain population groups. Variations in the *type of monomers* or their *amino acid sequence* change the O_2-binding properties of the Hb molecule, as do changes in the intraerythrocyte $[H^+]$ concentration (see fig 2-20). As each erythrocyte normally contains 200-300

million Hb molecules (99, 100), each of them has the capacity for binding approximately one billion (1 000 000 000*or* 10^9) molecules of O_2.

The energy requirement of erythrocytes is very small; they contain no mitochondria and use no O_2 for their metabolism. The energy necessary to maintain cellular integrity is derived from glycolysis, which means that they continuously produce lactic acid as the endpoint for their metabolism (101). The *leucocytes* of the blood, on the other hand, consume O_2, leading to a reduction of O_2 content in blood samples left for longer periods at room temperature. The amount consumed by normal amounts of leukocytes during the passage from lungs to tissues is so small, however, that *the mean O_2 content of blood leaving the left ventricle and that arriving at the tissues can be considered to be identical.* In severe leukemic leukocytosis, however, there may be a slight reduction.

The HbO_2 dissociation curve of normal adult arterial blood.

The bond between O_2 and the iron-containing *heme groups* (the HbO_2 *affinity*) is relatively weak; binding of O_2 molecules to Hb and releasing them is a continuous process. The mean number of O_2 molecules bound at any point of time, expressed as the SO_2 (see above), is determined by *i)* the density of O_2 molecules surrounding the Hb and *ii)* the Hb affinity for O_2. At a given temperature, the quantity of O_2 molecules is proportional to the pressure of O_2 (PO_2) dissolved as a gas in the blood.

If a blood sample is divided into a large number of aliquots, and each aliquot is equilibrated with a gas with a different PO_2, (but identical concentrations of CO_2), measurement of the SO_2 corresponding to the PO_2 in each aliquot gives a large number of PO_2/SO_2 combinations. When these are plotted into a coordinate system, traditionally with PO_2 on the x-axis and SO_2 on the y-axis, the points form an approximately S-shaped curve, the *oxyhemoglobin (HbO_2) dissociation curve* (fig. 2-19).

Factors that change the affinity state of Hb for O_2 change the shape of the curve and its position (see below). Such changes are often quantitated by the variations in the **P_{50}** value of PO_2, i.e. the PO_2 where *50% of the Hb molecules in a blood sample are saturated with O_2* (102, 103). The P_{50} value for normal adult blood is close to 3.5 kPa (26 mmHg) (103, 104).

Based on the shape of such curves, and assumptions about the co-operative nature of HbO_2 binding, scientists like Hill (105) and Adair (106) developed equations describing the HbO_2 curve for normal blood already during the first part of the twentieth century. Equations with correction factors to compensate for changes in pH, PCO_2, and blood temperature were later developed by Severinghaus (107), Kelman (108), as well as others. Such equations are often utilized to calculate the SO_2 corresponding to a given PO_2 value, and are reasonably accurate when the PO_2 is in the normal arterial range and the Hb and its surroundings are normal.

One of the major factors affecting the HbO_2 affinity, the intraerythrocyte 2,3 DPG concentration, is not routinely measured, making such equations inaccurate in some situations (e.g. in patients receiving massive transfusions with blood stored for more than 2-3 weeks (109)). Also, changes in the type of globins affect the characteristics of the HbO_2 curve (e.g. HbF, see below) and reduce the accuracy of SO_2 calculations. In addition, the equations are less accurate at the outer limits of the survivable pH range (110). Direct oximetric measurements of SO_2 is therefore preferable in blood from severely ill patients or when results are used for scientific purposes.

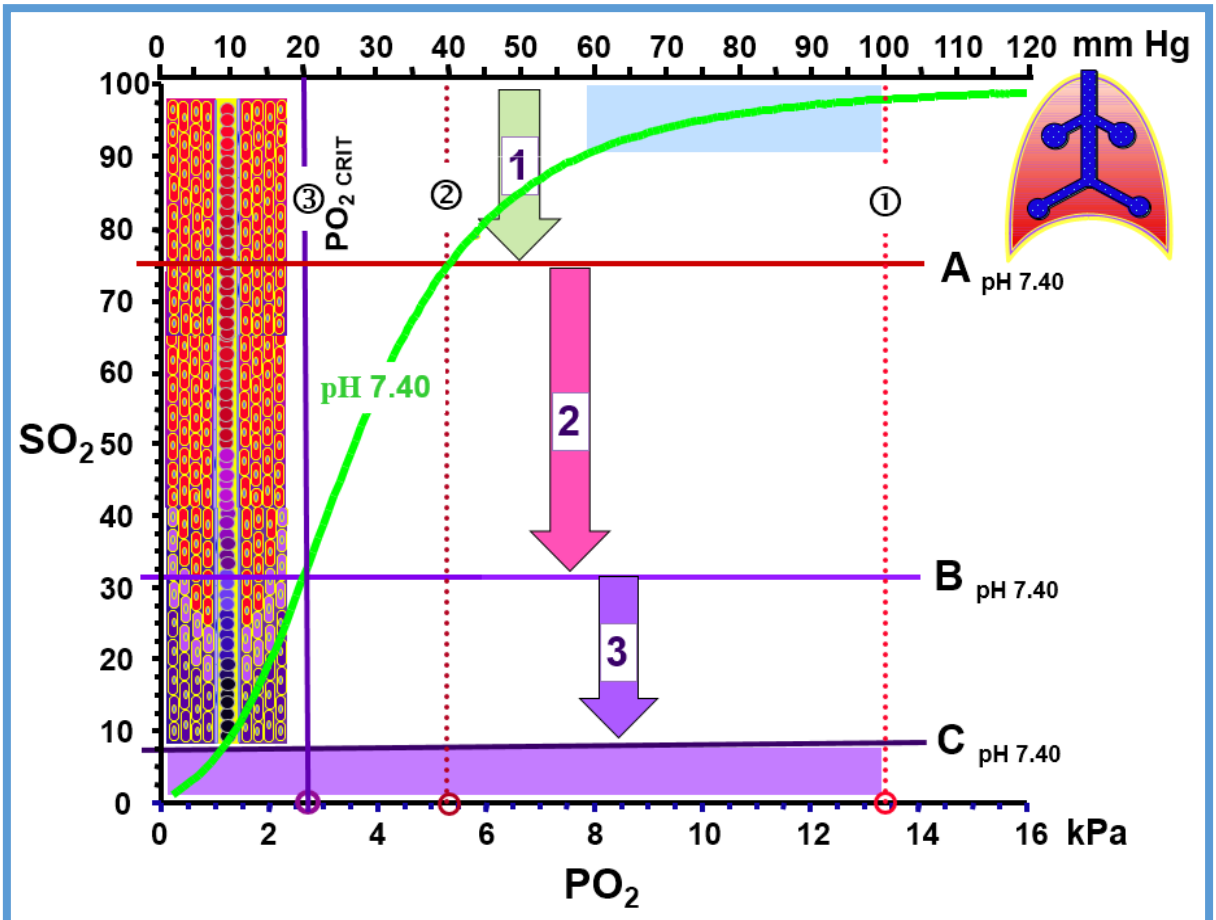

Figure 2-19. *The standard HbO_2 dissociation curve (green) for arterial blood with normal Hb* (**HbA**) *and pH. Vertical dotted lines (right to left) corresponds to ① Normal* **arterial PO_2** *(13.3 kPa) ② Normal mixed* **venous PO_2** *(5.3 kPa), and ③ Borderline critical PO_2* **($PO_{2\ CRIT}$)** *in venous blood draining individual tissues (2.7 kPa). Horizontal lines* **A**, **B** *and* **C** *are drawn from the intersection points between these lines and the HbO_2 curve. The light blue rectangle illustrate that the SO_2 stays above 90% until the PO_2 drops below 8 kPa. The green arrow* **(1)** *indicate the normal decrease in SO_2 from arterial to mixed venous blood; the red arrow* **(2)** *indicate the "reserve" capacity where the O_2 requirement of the tissues can be met by increased O_2 extraction at normal pH. The lilac arrow* **(3)** *indicate the area where a rightward shift of the HbO_2 curve (usually caused by acidosis, see fig 2-20) can still satisfy the tissue O_2 needs. Beneath line* **C**, *the PO_2 is below the critical level regardless of HbO_2 curve position and anaerobic metabolism becomes widespread.*

The **standard HbO_2 dissociation curve** (fig. 2-19) describes the SO_2 corresponding to any PO_2 value in arterial blood under normal conditions (i.e. pH 7.40, PCO_2 5.3 kPa *or* 40 mmHg, *and* normal erythrocyte levels of 2,3 DPG at 37° C (98.6°F)). The curve for normal mixed venous blood is shifted slightly to the right relative to the arterial one (see below), due to a modestly higher PCO_2 and H^+ concentration in end capillary, and thus venous, blood. The sigmoid shape of the curve favors optimal uptake of O_2 by the blood in the lungs, and the rightward shift of the more acid venous blood favors its subsequent release in the tissues.

The sigmoid shape is the result of the co-operative behavior between the monomers; the binding of an O_2 molecule to one of them changes the affinity state of the other three so that the whole molecule immediately becomes saturated after the first binding is completed (see above). Not all details of the mechanism for this co-operativity have been elucidated (111). Changes in the affinity of the heme groups for O_2 induced by the first binding is a common explanation

(106, 112); structural changes from tense to relaxed induced by either the first binding or by signals from other types of binding (heterotopic binding sites – see above and ref. 113) has also been postulated.

Three aspects of the normal HbO_2 curve shape (fig. 2-19) are of special clinical importance for optimal O_2 transport:

- A 40% reduction in P_aO_2, from the normal 13.3 kPa (100 mmHg) to 8 kPa (60 mmHg), reduces the S_aO_2 by only about 7.5% (from 97.5 to 91%). The consequence is that a moderate reduction in P_aO_2, resulting from pulmonary dysfunction or living at high altitudes, leads to only a modest reduction of the O_2 content of the blood (see O_2 content of the blood below).
- The *critical end-venous PO_2 in the microcirculation* is situated on the steep part of the curve and is assumed to be around *2.7 kPa (20 mmHg)* (see critical O_2 levels for tissue cells). The SO_2 corresponding to this PO_2 on the standard HbO_2 curve is 32%; i.e. only about 65% of the blood C_aO_2 would be available to the tissues before microcirculatory PO_2 became critical if pH, PCO_2, and temperature stay constant. Due to the HbO_2 curve shift (see below) caused by increased pCO_2 and H^+ in the blood during passage through the microcirculation, the SO_2 corresponding to the critical PO_2 in normal venous blood (and at the end of capillaries) under resting conditions is 3-4% lower than that of arterial blood. This effect is not depicted in figs 2-19 and 2-20, the importance of such shifts in microcirculatory blood is augmented by increased acidosis in tissues with increased metabolism or reduced O_2 supply.
- When cellular hypoxia occurs, increased production of lactic acid and/or accumulation of CO_2 in the microcirculation shifts the curve further to the right, which enables the blood to release more of its O_2 before the PO_2 becomes critical (fig 2-20). The amount of O_2 that can be delivered to the tissues *before* the critical end-venous PO_2 falls below the level where anaerobic metabolism starts, is the **effective DO_2**. It is important, however, to be aware that the value of **effective DO_2** represents a mean value for the resting organism. The critical effective DO_2 for individual organs is determined by the *local* tissue level of O_2 extraction vs. consumption *and* the ability of the organ to increase its perfusion (autoregulation of perfusion in the heart, brain, and others).

Changes in shape and position of the HbO_2 curve.

Changes in the concentration of various ions and molecules in the intracellular fluid surrounding the Hb molecules alters the shape and position of the HbO_2 curve. The standard sigmoid HbO_2 curve for normal arterial blood (fig 2-19) is only one of a large number of related curves found in man. **Physiological shifts** (see below for details and for pathological and inherited shifts) in both the shape and position of the curve may be due to

- Increased or decreased binding of H^+, CO_2, and 2,3 DPG by the Hb molecules.
- Changes in blood temperature.
- Binding of carbon monoxide (CO) to one or more of the monomers.
- Physiological variations in the chemical structure of the Hb molecule (variations in monomer composition, e.g. fetal Hb, HbF).
- Inborn variations, or spontaneous mutations, in the structure of the Hb molecule.

Of the major factors that cause shifts in HbO_2 curve position of normal blood within the physiological range, variations in H^+ concentration have the largest effect, followed by changes in blood temperature (114). The effects of variations in the H^+ concentration well within the survivable range (see fig 5-1) on the HbO_2 curve are shown in fig. 2-20.

- **Changes in H^+ concentration** (the *Bohr* effect) are by far the most common and important cause of HbO_2 curve shifts in acute and critical care medicine (115, 116). An *increased* H^+ concentration (i.e. decreased pH) reduces the HbO_2 affinity and shifts the HbO_2 curve to the right, while an *decreased* H^+ concentration (i.e. higher pH, as found in the tissue microcirculation when tissue hypoxia threatens) *increases* the affinity and shifts the curve to the left (fig. 2-20).
- **Changes in CO_2 concentration,** where an increased CO_2 level (in tissues) reduces the HbO_2 affinity and shifts the HbO_2 curve to the right, while a reduced CO_2 level (after excretion in the lungs) increased the HbO_2 affinity and shifts the curve to the left. Most of the CO_2 effect is mediated via its impact on the *intraerythrocyte H^+ concentration*; the direct impact of CO_2, which is mediated by the binding of CO_2 to Hb as carbamino compounds, is *per se* modest (114).
- **Changes in 2,3-diphosphoglycerate (2,3 DPG),** also called 2,3 Bisphospho-glycerate or *2,3 BPG) concentration* ni the erythrocytes affects the HbO_2 affinity; decreased levels of 2,3 DPG increase the affinity (left-shifted curve) and *vice versa*. The affinity increase induced by low levels (or absence) of 2,3 DPG is substantial (P_{50} changes from 3.5 kPa (26 mmHg) at normal 2,3 DPG levels (4 µmol/g RBC) to 2.0 kPa (15 mmHg) at 0.1 µmol/g RBC (117, 118). Variations within

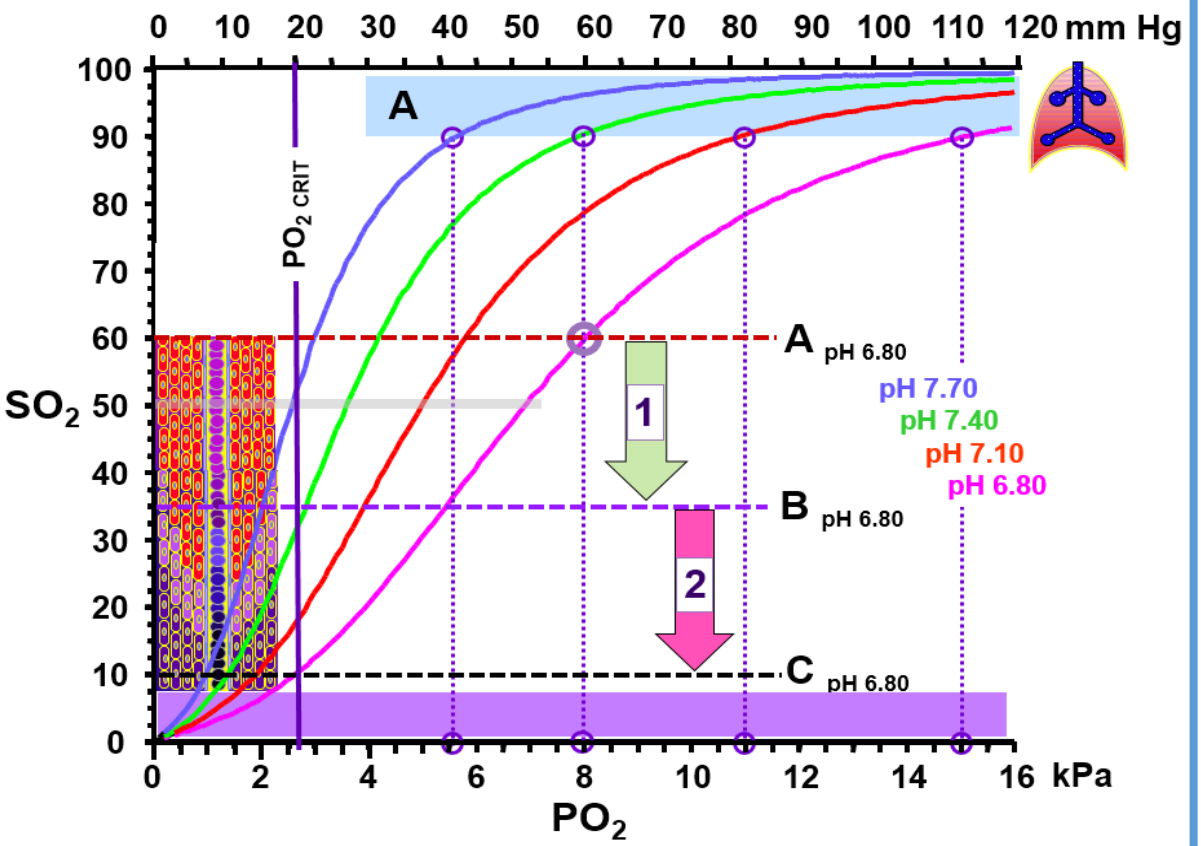

Figure 2-20. *HbO_2 dissociation curves corresponding to variations in blood H^+ concentrations. The blue field indicate a SO_2 between normal and 90%, the vertical dotted lines indicate the PO_2 where the curves for pH 7.70, 7.40, 7.10 and 6.80 results in a SO_2 of approximately 90%. The vertical dark lilac line indicate the critical end-venous PO_2 (**$PO_{2\ CRIT}$**) in the microcirculation; arrows **1** and **2** indicate the normal and the possible O_2 extraction, respectively (see also fig 2-19) at P_aO_2 = 8 kPa if the pH_a = 6.80. The PO_2 corresponding to the intersection between the curves and the horizontal grey line at SO_2=50% define the P_{50} value of each curve. The position of the HbO_2 curve for* **HbF** *at normal pH is slightly to the left of that drawn for pH 7.70.*

the normal range have, however, modest effects (114). Different units, such as 15 µmol/g Hb or 5 mmol/liter packed cells for normal levels, are used to describe the levels of 2,3 DPG.

- **Changes in blood temperature** also change the Hb affinity for O_2; *increased temperature decreases the affinity* (right shift of the HbO_2 curve) while a *low* temperature *increase* it (119). In one study, where P_{50} at **37°C** (98.6°F) was found to be 3.59 kPa (26.9 mmHg), P_{50} at **25°C** (77°F) was 1.67 kPa (13.2 mmHg), at **31°C** (87.8°F) 2.63 kPa (19.7 mmHg), and at **43°C** (109.4°F) 4.49 kPa (33.7 mmHg) (120). See fig. 2-21 for HbO_2 curves at different temperatures, based on values calculated using the equation proposed by Kelman and Nunn (108). The critical PO_2 for aerobic metabolism of the cells also decrease with sinking temperatures.

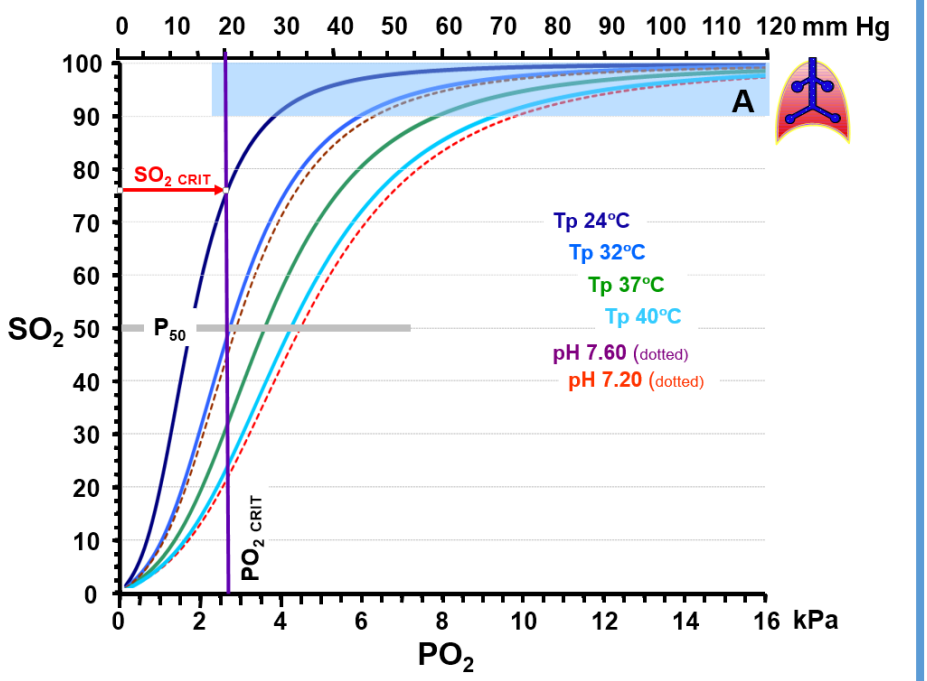

Figure 2-21. *Effect of temperature changes on the HbO_2 dissociation curve, compared to changes in pH at normal temperature. The curve at 37°C is representative for the "standard" curve; the effects on SO_2 for 32°C and 40°C is close (but not identical) to changes in the pH of 7.60 and 7.00, respectively. Note that at Tp 24°C, the critical PO_2 is reached at a saturation of approximately 75% (red arrow).*

The intraerythrocyte pH and 2,3 DPG content of erythrocytes are different from that of the surrounding plasma. Most investigators report an intra-erythrocyte pH that is between 0.20 and 0.30 lower than that in the blood (121); the plasma concentration of 2,3 DPG is negligible compared to the intracellular level. This is why free Hb in the blood (e.g. after pathological hemolysis) contribute little to the O_2 transport. Outside their normal erythrocyte environment, HbA molecules suspended in an artificial solution lacking 2,3 DPG have an affinity for O_2 far greater than that observed in blood (122). The P_{50} found for HbA under such conditions (0.77 kPa, 5.6 mmHg) corresponds to a HbO_2 curve shifted so far to the left that little O_2 is released from the Hb until the PO_2 is well below the value considered critical for venous blood draining the tissues. Also, free Hb molecules in plasma scavenge the important vasodilator nitrogen monoxide (NO); this may cause vasoconstriction and reduced tissue blood flow which accentuates tissue hypoxia.

Changes in intracellular pH, PCO_2, and blood temperature may occur virtually instantaneously; clinically relevant changes in 2-3 DPG levels normally takes several hours to days. The changes in P_{50} values induced by variations in pH may be large, from about 2.5 kPa (19 mmHg) in severe alkalosis (and in fetal blood) to 9.5 kPa (71 mmHg) in severe, but clinically relevant, acidosis (pH 6.30, ref 110).

Clinical consequences of Hb affinity changes and HbO_2 curve shifts.

Rightward HbO_2 curve shifts often have a beneficial effect on the *effective DO_2* (see above) but may also reduce it during conditions where P_aO_2 is subnormal (see below). Whether or not a curve shift increases or decreases the **effective DO_2** depends on which part of the elements in the DO_2 chain (Hb concentration, P_aO_2-SO_2, or C.O.) that have become dysfunctional or failed.

Effects of a rightward curve shift in arterial blood.

Positive. As a simple rule-of-thumb, a rightward curve shift increases the release of O_2 in the microcirculation; as venous blood is slightly more acid and contains more CO_2 than arterial blood, more O_2 is released (i.e. SO_2 becomes 3-4% lower) in the microcirculation than the amount calculated from the standard arterial HbO_2 curve. In *severe acidosis* (fig. 2-20) this effect may increase the *effective* DO_2 by 20% or more at a constant C.O. as long as the P_aO_2 is high enough to result in a normal S_aO_2. At a pH of about 6.30 (the lowest reported value compatible with survival is 6.33 (123)), the PO_2 necessary to obtain a SO_2 of 90% is about 20 kPa (150 mmHg), and about 30 kPa (225 mmHg) is necessary to obtain a normal SO_2 of 97.5%. On the other hand, the "critical" PO_2 of 2.7 kPa (20 mmHg) at a pH of 6.30 corresponds to an SO_2 of 7-8% (110); i.e. in extreme acidosis, almost *all* (around 90%) the O_2 present in the blood can be extracted before the microcirculatory PO_2 becomes critically low.

Negative. On the negative side, a rightward shifted curve decreases the SO_2 (i.e. the O_2 content of the blood) in the lung capillaries (fig. 2-20), and thus in the arterial blood. Except for in extreme acidosis, this effect is of modest importance as long as the PaO_2 is in the normal or supernormal range. In respiratory failure, or when breathing gas with a reduced PO_2, the rightward shift of grave acidosis can, however, reduce the SO_2 by about 50% of that corresponding to a normal HbO_2 curve, creating life-threatening hypoxemia (124). At a pH of 6.30 (see above), a normal arterial PO_2 of 13.3 kPa (100 mmHg) corresponds to an SO_2 of approximately 75% (110), i.e. a close to 25% reduction in the C_aO_2.

Effects of a leftward curve shift in arterial blood.

Positive. A leftward HbO_2 curve shift has the opposite effect on the oxygenation of blood in the lungs; a satisfactory S_aO_2 can be attained at a much lower PO_2 than normal (fig. 2-20).

Negative (?). On the other hand, if the curve stays leftward shifted also in the microcirculation, less of the delivered O_2 can be released before the PO_2 becomes critical. If this leads to tissue hypoxia, however, local accumulation of CO_2 and/or lactic acid in the cells causes increased amounts of H^+ to diffuse into the microcirculation. The effect of increased capillary CO_2 and H^+ shifts the HbO_2 curve in the local microcirculation rightward, increasing the O_2 release in tissues where the O_2 supply becomes critical.

Effects of local HbO_2 curve shifts in the microcirculation.

If the locally generated lactic acid becomes metabolized by other organs, so that general lactic acidosis does not occur, the arterial blood may maintain a normal or even a left-shifted dissociation curve. The blood that arrives at the tissues may then have a high S_aO_2 *and* release more of its total oxygen content; the increased O_2 extraction gives a lower SO_2 in the venous blood that drains such organs.

Under conditions when the PO_2 of the blood is critically low, such as during catastrophic *lung failure*, in babies *during delivery*, or at very *high altitudes*, the O_2 content of the blood and O_2

delivery to the tissue can be optimized by a leftward HbO_2 curve shift in the blood perfusing the lungs. Increased lactate production in the tissues of such persons means that the oxygenation of many tissue cells is critical and that danger of hypoxic tissue damage may be imminent.

The optimal condition of the HbO_2 curve shifts.

The optimal situation for O_2 transport would be an HbO_2 curve that is strongly left-shifted during passage through the lungs and with an equally strong right shift during passage through the microcirculation. This situation exists to a modest degree under normal conditions, due to the difference in pH and PCO_2 in the systemic and pulmonary microcirculation. It is more pronounced during delivery, where the high content of HbF in the baby's blood cause a left-shifted curve and a high SO_2 despite low PaO_2 (fig. 2-20), and during high altitude mountaineering, where a chronic respiratory alkalosis shifts the curve to the left but hypoxemia create *local acidosis in skeletal muscles* without creating a generalized lactacidosis (125). Also, the curve for stored blood becomes increasingly left-shifted with storage time due to loss of intraerythrocyte 2,3 DPG (see below); after massive transfusions of such blood, the mean HbO_2 curve for the circulating blood becomes left-shifted. This shift can, however, be partly reversed by acidosis (109).

Effect of storage on bank blood.

Erythrocytes with normal HbA stored in blood banks gradually become depleted of 2,3 DPG; after two or more weeks, there is a 65 to 85% reduction (126) and the blood develops a higher affinity for O_2 (a *left-shifted* HbO_2 curve). This can be compensated for by increased acidity in tissues where the O_2 supply is critically low, increased $[H^+]$ shifts the curve back to the normal position (or to the right, depending on how acid the blood has become). In laboratory animal experiments, fresh blood seems to be superior to stored blood (127). In clinical investigations, however, transfusion of stored bank blood does not seem to be inferior to fresh blood (128, 129, 130, 131). In addition, part of the beneficial effect of increasing the erythrocyte concentration may be the concomitant increase in viscosity, which may help to keep the microcirculatory vessels open and perfused during shock states (77). The 2,3 DPG content of stored erythrocytes is slowly restored after transfusion, after between 4 hours (132) to 7 hours (133), around 50% of normal levels of 2,3 DPG have been regenerated. It may take several days, however, before the levels are all the way back to normal (134).

VARIATIONS IN HAEMOGLOBIN STRUCTURE AND FUNCTION

Fetal hemoglobin

The fetal blood Hb (HbF) produced during gestation has a higher O_2 affinity than that of adult HbA, shifting the $HbFO_2$ curve to the left. The P_{50} of pure fetal blood is about 2.5 kPa (18.3 mmHg) (135), while arterial blood at birth, consisting of a mix of HbF and HbA, has a P_{50} of about 2.8 kPa (21-23 mmHg) (136, 137). The position of the HbO_2 curve for fetal blood, and bank blood stored for more than 2.5 weeks, are both slightly to the left of that corresponding to normal blood with a pH of 7.70 (fig. 2-20), a pH value that can be found under extreme hyperventilation during high altitude ascent (138). The leftward shift of HbF is not due to the change in the molecular configuration *per se*, but to a reduced effect on the Hb molecule in response to the binding of 2,3 DPG (139). Mean PO_2 in premature babies during delivery is about 3.15 kPa (23.6 mmHg) (140), due to the left-shifted HbO_2 curve for fetal blood, this will give a S_aO_2 of 65-70%. This value agrees well with measurements showing a mean S_pO_2 of 66% during the first minute after birth (141).

Genetic variations among hemoglobins (Variant hemoglobins).

Variations in the chemical structure of the Hb molecule (i.e. variant Hb, see below) can be due to genetic changes in the chemical structure of the globins monomers (i.e. the amino acid sequence), *or* to the assembly of the Hb monomers to the tetramer.

Structural changes in the Hb molecule due to mutations (usually hereditary) can shift the shape and position of the HbO_2 curve in both directions; variants with a P_{50} as low as 1.5 kPa (12 mmHg) and as high as 9.3 kPa (70 mmHg) has been described (142). The former is considerably lower than that of HbF (see above); the latter is close to that of normal HbA at a pH of 6.30 (110). Mutations leading to increased affinity (left-shifted HbO_2 curve, i.e. a P_{50} lower than 3.5 kPa (26 mmHg)) occur more frequently than the opposite. Some variations would be lethal if the blood contained only such changed molecules; as long as they represent only a modest fraction of the total number of Hb molecules, however, the consequences may be small and of little clinical importance. More than 1 000 mutations leading to changes in the affinity of Hb molecules to O_2 have been described (143).

Persons who have Hb variations with increased O_2 affinity often have a high Hb but are otherwise healthy and live normal lives. Those with variations that cause a decreased O_2 affinity (right-shifted curve) may have anemia and/or a reduced SO_2; most of these also usually live normal lives (144). It is conceivable that those with more extreme deviations die before, or during, delivery. In those with a right-shifted curve, the diagnosis is often revealed by chance when an unexpectedly low S_pO_2 is observed in patients found to have a normal P_aO_2. Not all such patients will show an agreement between S_pO_2 and the S_aO_2 measured by the co-oximeter of a blood gas machine (145). The variant Hbs differ in their response to H^+ and 2,3 DPG; some show a reduced effect while others exhibit no change of affinity for O_2 (146, 147).

Most such inherited variants of Hb structure affect only a very limited number of families. The two major exceptions to this are the inherited diseases *Thalassemias* and *Sickle Cell Disease*, which affect millions.

Thalassemias consist of a group of diseases where dysfunction in the synthesis of α- globins (α-thalassemias), β-globins (β-thalassemias), or both, lead to the creation of incomplete or faulty globins and thus of the Hb tetramer. The most common consequence in those who survive gestation are anemia and hemolysis of varying severity (143). The consequences for HbO_2 affinity vary with the type of disease, in most variants the affinity is close to normal.

Sickle Cell Disease (SCD) is an inherited blood disorder that is common in Central Western Africa and can also be found in all parts of the world where persons of West African descent reside (143). The Hb molecules of patients with sickle cell disease (**HbS**) have one amino acid substitution; one glutamic acid in the β hemoglobin chain is substituted with valine (148). In some persons, the *homozygotes*, nearly all the hemoglobin's are HbS; in others, the *heterozygotes*, HbS constitutes 30 to 40% of the total. The patients often have anemia; the most dangerous consequence of the disease is that the HbS polymerizes when deoxygenated, creating stiff chains of Hb molecules which results in sickle-shaped erythrocytes whose flexibility in the microcirculation is lost. In patients with a high percentage of HbS, this may lead to widespread destruction of the erythrocyte cell membrane with the release of free hemoglobin, *plus* vascular occlusion and tissue ischemia when aggregates of poorly deformable erythrocytes fail to pass through the microcirculation.

The affection of the lungs with oxygenation problems, pulmonary infiltrates, and fever (Acute chest syndrome, ACS, *or* Sickle Cell crisis) is the second most common cause of hospitalization in SCD (next after vaso-occlusive crises in the systemic vasculature). As the occurrence of ACS is also associated with an increased risk of chronic lung disease, it is the most common cause of death in young men with SCD (149, 150). In these patients, the HbS is not only a carrier of O_2 but also a source of microcirculatory ischemia due to its obstructive properties.

The risk of life-threatening complications is reduced if early treatment of the SCD complications is instituted promptly when the first symptoms of an incipient sickle cell crisis occur (151). The most important components of early therapy for incipient SCD/ACS are ***i)*** sufficient oxygenation of arterial blood, ***ii)*** optimization of hydration to ensure adequate tissue blood flow, and ***iii)*** red cell exchange-transfusion as early as possible (152). In patients with homozygote disease, crises may lead to serious disease and may be lethal if not treated swiftly. In Sickle Cell Disease, the affinity for O_2 is decreased and the HbO_2 curve is shifted to the right (153); this effect is, however, not caused by the HbS itself, but by an increased amount of 2,3 DPG in the erythrocytes containing HbS (154).

Pathological changes in the O_2-binding capacity of normal Hb.

See also Part 5-4 for laboratory diagnosis and blood gases.

The most common cause of such changes is the inhalation of carbon monoxide (CO) gas and inhalation/ingestion of agents containing nitrogen oxides (NO_x) or other oxidizing agents (see below). As such agents are produced endogenously in small amounts also under normal conditions, some of the Hb molecules in normal blood of healthy persons (typically around 0.5% carboxyhemoglobin (COHb) and 1.5% methemoglobin (MetHb) (155)) have pathological O_2-binding characteristics. The consequences of such low levels for O_2 transport are negligible, but high levels resulting from intoxications may be life-threatening or fatal. Sulfur-containing agents or drugs (toxic agents like hydrogen sulfide and some antibiotics) may, in some susceptible individuals, bind irreversibly to Hb (SulfHb), which inhibits its binding of O_2. There is no effective treatment for this condition, which fortunately is rare.

Carboxyhemoglobin (COHb).

Carbon monoxide interferes with the O_2 transport by displacing O_2 from the heme sites of the Hb molecule (156). Carbon monoxide has an affinity for these sites more than 200 times that of O_2, (218 times at body temp and independent of pH within the physiological range (157)); inhalation of gas containing low levels of CO may cause serious reductions of the O_2 transport capacity of the blood. With constant exposure, the gas accumulates in the blood over time, and a low concentration of 500 ppm (0.05%) of CO in the inspired air, inhaled for 30 minutes, increases the COHb to about a fraction of 0.08 or 8%. Exposure to the same concentration for 3 hours, however, increases the COHb levels to about a fraction of 0.4 or 40% (158).

This level represents a more serious reduction in tissue oxygenation than what would result from a similar reduction of O_2 content due to anemia (see below). Such patients do not become cyanotic, as the Hb binding sites for O_2 are not vacant (as in the deoxy confirmation, see above), but *may* rather have a rosy or cherry red color of the skin and mucosal membranes even when hypoxemia is life-threatening. Such coloring may, however, not be noticeable even in severely CO-intoxicated patients (159); its absence cannot rule out CO intoxications.

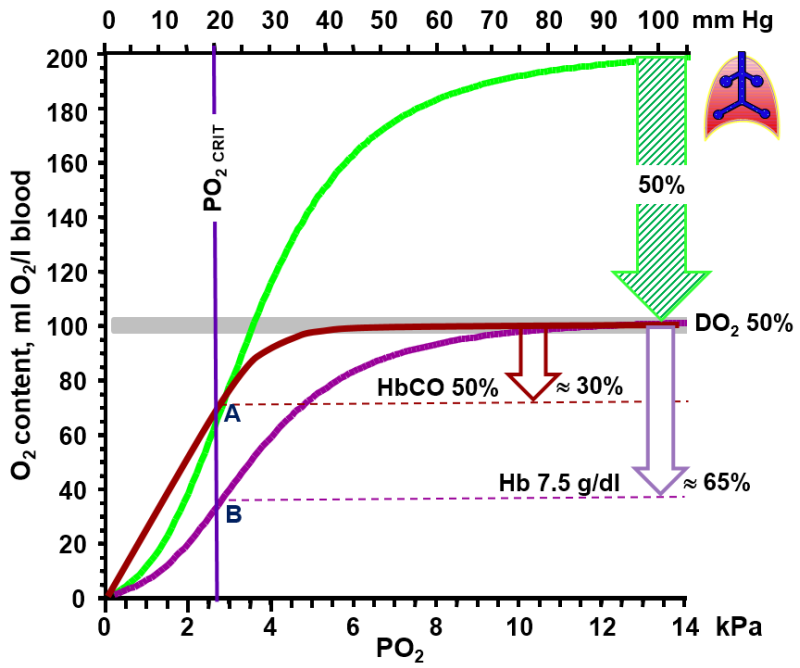

Figure 2-22. *Consequences of a 50% reduction in DO_2 due to either anemia or CO intoxication. Note that the Y axis shows the content of O_2 in ml O_2/l blood.* **Green curve:** *Normal conditions in arterial blood (Hb 15 g/dl).* **Brown curve:** *50% HbCO.* **Lilac curve:** *Hb 7.5 g/dl. The vertical line denote the critical microcirculatory PO_2, horizontal dotted lines represent the intersection between this line and the curve for HbCO* **(A)** *and for anemia* **(B)**. *The amount of O_2 released from blood with 50% HbCO before the critical microcirculatory PO_2 is reached is about 30% of the C_aO_2, compared to about 65% for anemia.*

Increased levels of COHb cause a proportional decrease in HbO_2; at 40% COHb, the HbO_2 is reduced to about 60% of normal. This situation is more critical than that caused by a 40% reduction in Hb, as the binding of CO to one or more Hb monomers changes the affinity for O_2 of the remaining monomers. The HbO_2 dissociation curve becomes left-shifted (even more than the curve representing normal blood at pH 7.70 – see fig. 2-22) and Hb releases less O_2 in the microcirculation. If the HbCO is 40%, more than 60% of the O_2 in the blood remains bound to Hb molecules when the tissue critical PO_2 of 2.7 kPa is reached (160). CO may also inhibit mitochondrial function, reducing the ability of the cells to utilize O_2 (161); the importance of this mechanism for the cerebral toxicity of CO and the benefits of delayed hyperbaric O_2 treatment is, however, debated (162).

As the binding of CO to heme groups is competitive, treatment consists of *i)* increasing the number of O_2 molecules, and *ii)* reducing the number of CO molecules in the fluid surrounding the Hb molecules. When the O_2/CO ratio is high enough, a CO molecule that leave a heme group will be replaced by O_2, despite the difference in affinity. Acute treatment thus consists of administering O_2 as soon as possible, using supply devices that delivers as high F_iO_2 as possible, preferably devices that ensure a F_iO_2 of 1.0 (see also Part 4-4, Oxygen therapy). Inhalation of gas with pure O_2 reduces the mean half-life of COHb from 320 min to 74 min. Increasing the density of O_2 molecules in plasma further by hyperbaric O_2 treatment further reduces the mean half-life of COHb to 23 min (163), the latter treatment is, however, difficult to implement in a pre-hospital setting. Increasing the excretion of CO by increasing the ventilation volumes also shortens the half-life substantially (164). Such treatment requires that reduction in CO_2 and respiratory alkalosis (Part 5-3) is avoided, as this may aggravate the leftward shift of the HbO_2 curve. Admin-istering a gas mixture containing O_2 and CO_2 was previously utilized in the acute treatment of CO intoxications; this practice was discontinued after it was found that it may cause CO_2 accumulation in the blood and severe acidosis if the patient's capacity for spontaneous ventilation was already compromised. In others, however, it may be advantageous.

Methemoglobin (MetHb).

Oxidation of the bivalent (ferrous, Fe^{++}) ions of the heme groups to trivalent iron (ferric, Fe^{+++}) create methemoglobin (MetHb), which leaves the heme group of the affected monomers unable to bind O_2. As for heme groups occupied by CO, these monomers do not participate in O_2 transport. The oxidation also changes the chemical structure of the affected monomers; if the Fe^{++} of one or more of the four Hb monomers is oxidized to Fe^{+++}, the HbO_2 affinity of the heme sites of the remaining monomers increases, shifting the HbO_2 curve for whole blood to the left (165).

Increased MetHb may be due to congenital diseases; the vast majority of cases occur, however, after inhalation or ingestion of, or skin contact with, certain toxic agents (166). These patients may become cyanotic when the MetHb levels increase above 10%.

Standard therapy is an infusion of methylene blue, which reduces the Fe^{+++} back to Fe^{++}; in some patients, such treatment has little effect. An alternative may then be infusions of n-acetyl cysteine, NAC (167) – in doses similar to those used in the treatment of paracetamol/acetaminophen poisoning.

TRANSPORT OF GASES BY THE BLOOD

OXYGEN FROM THE LUNGS TO THE MICROCIRCULATION

The O_2 molecules in the blood are present as *either* dissolved gas *or* Hb-bound O_2, these are at all times in equilibrium with each other. The equilibrium shifts in response to changes in the Hb molecule environment as well as the structural molecular changes described above.

- **The free O_2 molecules in gaseous form** are dissolved (see also Apx) in the fluid phase (plasma *and* intra-erythrocyte fluid) of the blood, and the number of free O_2 molecules present in the blood determines the O_2 pressure (PO_2). The relationship between the amount of dissolved O_2 and PO_2 in the blood at a given temperature is *linear*. In normal arterial blood with a Hb=15 g/dl, the number of free O_2 molecules represents ≈1.5% of the total O_2 content; in mixed venous blood, it represents 0.7-0.8% (see "Extreme state" below).
- **The O_2 molecules that are reversibly bound to the hemoglobin (Hb) molecules** suspended in the fluid inside the erythrocytes represent the remaining 98.5% of the O_2 in the normal arterial blood. The relationship between HbO_2 and PO_2 in the blood is *non-linear* and is described by the HbO_2 dissociation curve (fig 2-19 above).

The **sum of O_2 molecules in the two states** represents the **total O_2 content** (C_aO_2) in the arterial blood.

THE O_2 CONTENT OF ARTERIAL BLOOD (C_aO_2).

The extreme state: the O_2 dissolved in blood without functional hemoglobin.

A. When breathing room air at normal atmospheric pressure.

Oxygen has low solubility in plasma; the O_2 content of the fluid phase of the blood at 37°C is only **0.225 ml/l per kPa** *or* **0.03 ml/l per mmHg** (168, 169). A person with normal lung function, breathing air at sea level, has an arterial PO_2 around 13.3 kPa (100 mmHg). The **volume of O_2 gas dissolved per liter of blood devoid of functioning Hb at normal temperature** (i.e. in plasma and intraerythrocyte fluid) is then

0.225 ml O_2/l/kPa x **13.3** kPa *or* **0.03** ml O_2/l/mmHg x **100** mmHg = **3 mlO_2/l,** about 1.5% of that in blood with normal Hb (see below).

B. When breathing 100% O_2 (F_iO_2=1) at normal atmospheric pressure. Under such conditions, the P_aO_2 may theoretically increase to 90 kPa (675 mmHg) after complete de-nitrogenation of the blood; it may even be slightly higher if hyperventilation leads to a very low PCO_2 (see Part 4-1, alveolar air equation). In a person with perfect lung function, the content of dissolved O_2 in one liter of blood would then be

0.225 mlO_2/l/kPa x **90 kPa** *or* **0.03** mlO_2/l/mmHg x **675** mmHg, **= 20.25 mlO_2/l,** about 10% of that in blood with normal Hb.

C. When breathing gas at supernormal (hyperbaric) pressures.

During diving, and in hyperbaric chambers, breathing 100% O_2 at three atmospheres (≈304 kPa *or* 2280 mmHg) may secure adequate tissue oxygenation in the absence of functioning Hb. Under such conditions, the alveolar PO_2 can theoretically increase to almost 300 kPa; in a person with perfect lung function, the arterial PO_2 would be approximately the same. The volume of O_2 gas dissolved in each liter of blood is then

0.225 mlO_2/l/kPa x **300 kPa** *or* **0.03** ml O_2/l/mmHg x **2250** mmHg **= 67.5 mlO_2/l,** about 34% of that in blood with normal Hb.

A C.O. of around 4 l/min would be sufficient to cover the resting $\dot{V}O_2$ of the tissues (67.5 ml O_2/l x 4 l/min = 270 ml O_2/min); under such conditions, survival is possible without any functioning Hb. Consequently, a strategy of using hyperbaric oxygenation has been advocated as an emergency treatment when severe carbon monoxide (CO) poisoning inhibits the O_2-carrying function of Hb (170); it has also been tried in many other conditions, including acute severe anemia (171). The logistics of establishing such treatment in a pre-hospital or acute care setting are, however, daunting, especially if the patients also need advanced supportive treatment.

Another impediment to continuous hyperbaric O_2 treatment is that arterial PO_2 at such high levels can be tolerated only for a limited time (minutes to a few hours), as they are toxic not only to the lungs but also to the brain (see Oxygen toxicity above). Thus, in the absence of Hb, the human organism can function only under conditions with high ambient pressure and breathing pure O_2, and then only for a limited time. A species of cold-water fish ("icefish") survive without any Hb, to compensate for this, they have a heart size relative to body mass about 5 times that of other fish (see also fig 2-25).

High-pressure O_2 breathing for limited periods is, however, an established treatment of air embolization in diving accidents (172, 173); the major goal of such treatment is to reduce the size of air bubbles in the circulation and increase the speed of their resolution. It is also, to some extent, used in-hospital in patients with CO intoxications to reduce delayed cerebral damage. The beneficial effects of hyperbaric O_2 in the latter state are uncertain (162, 174).

The normal state: C_aO_2 in blood with normal hemoglobin.

From the above, it is clear that the amount of O_2 dissolved in the circulating fluid cannot alone sustain aerobic metabolism in humans or other complex organisms for extended periods. All warm-blooded higher organisms are therefore equipped with hemoglobin (see above), whose chemical structure and functional properties are adapted to the O_2 content of the ambient environment of the species (175).

The O_2 binding capacity of Hb: Hüfner's constant.

The chemist Hüfner found, in experiments using horse blood, that **each gram of Hb could bind 1.34 ml of O_2** when fully saturated; this value is called *Hüfner's constant*. It has later been established that one gram of the most common type of Hb in humans, **HbA,** can bind **1.39 ml O_2** when fully saturated (176); this value has therefore been used by some researchers when calculating the **C_aO_2**. The blood of most persons does not, however, contain only pure HbA; it also contains small amounts of other Hb variants (e.g. HbF, HbA_2, etc. – see Hb above). In addition, it also contains Hb molecules whose ability to bind O_2 is changed by endogenously produced nitrates (methemoglobin, MetHb) (177) or carbon monoxide (HbCO); both of which are present in small quantities (0.5% to 1.5% in non-smokers) under normal conditions (178). Values of O_2 binding to Hb reported in blood from volunteers, therefore, vary between 1.37 and 1.30 ml/g Hb (179, 180); the value most often quoted as clinically relevant for blood in most persons is the value of 1.34 ml O_2/g Hb originally found by Hüfner (181, 182, 183). Accordingly, this value is employed for calculations of O_2 transport in this compendium.

Under normal circumstances, not all of the Hb molecules within an erythrocyte are saturated with O_2 (see above). The amount of O_2 carried by the Hb is close to proportional to the oxygen saturation (SO_2) of the blood; which preferably should be measured directly by a co-oximeter when accuracy is needed (see Part 5-4). *Calculations* of SO_2, based on PO_2, blood pH, PCO_2, and temperature, may have a satisfactory clinical accuracy when normal arterial blood has a normal or high PO_2. Such calculations may, however, be *inaccurate*, or even grossly erroneous, in some patients; variations in 2,3 DPG content and/or the presence of increased COHb, methemoglobin, variant Hbs, etc. (see above) are common sources of error.

Calculating the O_2 content of normal arterial blood (C_aO_2).

The content of O_2 in one liter of normal human blood is calculated as

C_aO_2 = [(Hüfner's constant (in mlO_2/g Hb) **x gramHb/l x fraction of HbO_2** (relative to all Hb, as $\%SO_2/100$)**) + (Dissolved O_2/l/kPa x PO_2)]**

If we use the Hüfner's constant of 1.34 ml O_2/gHb for fully saturated Hb, the constant for dissolved O_2 = 0.225 mlO_2/kPa/l (see above),*and* assume a normal Hb = 15 g/dl (150 g/l), P_aO_2 = 13.3 kPa and S_aO_2 97.5%,

THE OXYGEN CONTENT OF ONE LITER OF NORMAL ARTERIAL BLOOD is

[(1.34 mlO_2/gHb x 150 gHb/l x 97.5/100)) (bound to Hb) **=196 mlO/l**	**+**	**(0.225 mlO_2/l/kPa x 13.3)]** (dissolved as gas) **3 mlO_2/l**

A total of 199 mlO_2/l *or, for simplified bedside calculations*, approximately **200 mlO_2/l.**

Consequently, **in the absence of severe anemia**, the overwhelming part (approximately 98.5%) of the oxygen in arterial blood is bound to hemoglobin. In most clinical situations, provided normally functioning Hb, the **oxygen content of the blood can be assumed to be proportional to the Hb and its SO_2** (see also the graphic presentation in fig. 2-23). A bedside simplification of the above equation, using 1.33 mlO_2/gHb instead of Hüfner's 1.34 mlO_2/gHb, allows calculation of the *approximate* C_aO_2 in a liter of blood as

C_aO_2 (mlO_2/l) ≈ (Hb + ⅓Hb)g/dl x S_aO_2/10.

With Hb = 15g/dl and S_aO_2 = 97.5%: (15+5) x 9.75 = 195 mlO_2/dl blood, an error of about 2%.

THE OXYGEN DELIVERY (DO_2) TO THE TISSUES

Calculation of DO_2.

The DO_2, i.e. the total amount of O_2 supplied to the whole organism, is the product of the O_2 content of arterial blood and the total blood flow (cardiac output, **C.O.**) to the organism:

$DO_2 = C_aO_2$ x C.O.

With a normal C.O. of 5 liters, and breathing normal air at sea level, the volume of **O_2 supplied to the organism per minute** as dissolved gas *and* Hb-bound O_2 (**DO_2**) is

(196 mlO_2/l *(bound)* **+ 3 mlO_2/l** *(dissolved)* **)x 5 l/min ≈ 1 000 mlO_2/min**
(or 44.6 mmol/min), a value about **4 times** that of normal **resting $\dot{V}O_2$.**

As the baseline C.O. of 5 l/min usually refers to a 70 kg person of normal build (see below), the **normal DO_2 is about 14.3 ml/kg.**

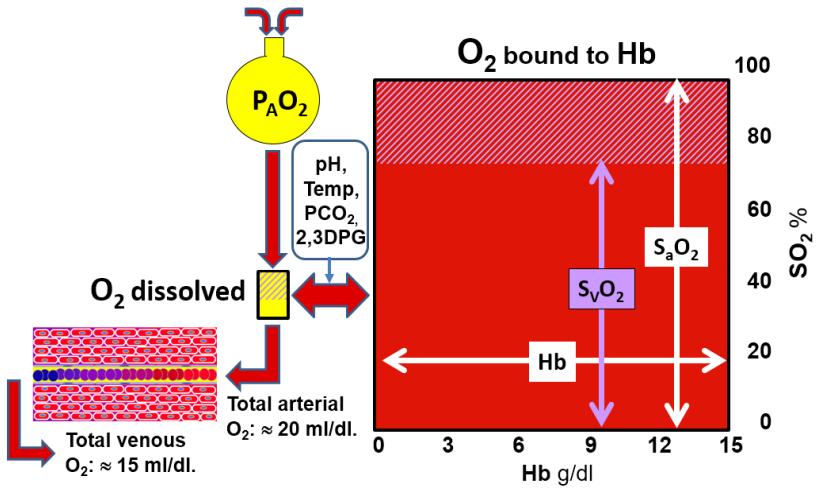

Figure 2-23: *Transport of O_2 by arterial blood. The equilibrium between PO_2 (dissolved O_2, yellow rectangle) and HbO_2 saturation (red square) is determined by the four factors shown in the drawing. The area of the squares is representative for the normal amounts of O_2 in the two states in arterial blood. Hatched areas indicate normal resting difference between arterial and venous blood.*

In otherwise healthy persons, a *reduced* C_aO_2 is, up to a certain limit, compensated for by a combination of an **increase in C.O.** and increased **extraction of O_2** from the blood (see also fig. 2-19). When the cause of **DO_2** reduction is a failure to maintain a normal C.O., however, increasing the C_aO_2 by increasing the Hb has major limitations and may even have negative effects on the circulation (see Part 2-2).

The mean *resting* C.O. is often given as ≈ 5 L/min (184, 185, 186). In many types of investigations, especially in sports medicine, the test persons are not at complete rest during the "control" or "baseline" phase of the experiment, the baseline C.O. is then higher than the true resting volume. The mean C.O. values calculated from a large number of studies including individuals between 18 and 55 years of age was found to be in the range of 6.4-7.0 l/min (CI 3.4-3.8 l/min/m^2, men) and 5.9–6.3 l/min (CI 3.6–3.8 l/min/m^2, women) (187). This illustrates the danger of including studies reporting "baseline" values and true resting values in the same analysis.

Effect of breathing 100% O_2 on the C_aO_2 at normal Hb levels.

Breathing 100% O_2 (F_iO_2 = 1) with normal lung function at sea level has a modest effect on the C_aO_2, as the maximum theoretical increase in S_aO_2 is about 2.5% and the amount of

dissolved O_2 is small compared to that bound to Hb (see above). Assuming a maximum **P_aO_2 of 90 kPa** or 675 mmHg (see above and Part 4-1) and a normal HbO_2 curve, the equation becomes

C_aO_2 = [(1.34 mlO_2/g Hb x 150 g Hb/l x 100/100) + (0.225 mlO_2/l/kPa x 90)]
= 201 ml O_2/l *(bound)* **+ = 20 ml O_2/l** *(dissolved)*

A total of 221 ml O_2/l blood, or a C_aO_2 **increase of about 11%** compared to room air.

Breathing 100% O_2 (F_iO_2 = 1) with dysfunctional lungs. In persons with *moderately dysfunctional lungs* at sea level, or with *normal lung function at high altitudes,* breathing 100% O_2 can result in a significant increase in the C_aO_2 (see also Part 4-4). If the PO_2 is **6 kPa** (**45 mmHg**) when breathing normal air, the expected SO_2 with normal HbO_2 affinity is around 80% (see fig. 2-19). The O_2 content equation is then

C_aO_2 = [(1.34 ml O_2/g Hb x 150 g Hb/l x 80/100)) + (0.225 mlO_2/l/kPa x 6)]
= 161 ml O_2/l *(bound)* **+ = 1.4 ml O_2/l** *(dissolved)*

A total of 162.4 ml O_2/l blood, about **20% lower** than normal.

If breathing O_2-enriched air **increases the P_aO_2 from 6 to 10 kPa** (75 mmHg), the S_aO_2 will be approximately 95% and the equation becomes

C_aO_2 = [(1.34 mlO_2/g Hb x 150 g Hb/l x 95/100)) + (0.225 mlO_2/l/kPa x 10)]
= 191 *(bound)* + **= 2.25** *(dissolved)*

A total of 193.5 ml O_2/l blood, about **3% lower** than normal.

See also fig. 2-24 for the relationship between PO_2 and C_aO_2 for three different levels of Hb. In persons where intrapulmonary shunts are the predominant derangement, increasing the F_iO_2 has only minor effects on the C_aO_2 (see Part 4-4, fig 4-28).

Effect of anemia on DO_2.

The **ultimate anemia** is a state where **no functional Hb** is present in the circulating blood (see extreme state above). Given a resting C.O. of 5 liters, the volume of O_2 that can be supplied to the organism purely as dissolved gas when **breathing room air** at sea level is

DO_2 = 0.225 mlO_2/l/kPa x 13.3 kPa x 5 l/min **=14.96 mlO_2/min** *or* approximately **15 mlO_2/min.**

This DO_2 represents *approximately* **6% of the normal resting O_2 consumption**; a **C.O. of almost 85 l/min** would be needed (calculated as: 0.225 ml O_2/l/kPa x 13.3 kPa x 85 l/min= 254 ml O_2/min) to supply the 250 ml O_2 required for aerobic metabolism. Such a C.O. is about 3.5-4.0 times higher than the maximum attained by top-trained athletes (188, 189) and is impossible to achieve (see also below).

When **breathing pure O_2,** the amount of dissolved O_2 becomes about **20.25 mlO_2/l** blood (see calculations above). This represents an increase to **almost 7 times** from that breathing room air. A C.O. of approximately **13 l/min** could then theoretically satisfy the body's O_2 requirements, calculated as

DO_2 = 0.225 mlO_2/l/kPa x 90 kPa x 13 l/min = **263 mlO_2/l.**

The myocardium has, however, a much higher O_2 consumption than the rest of the body (see fig. 2-8 above) and would be the first organ to become incapacitated by hypoxia due to insufficient O_2 supply. It is inconceivable that a C.O. of this magnitude could be mounted under such conditions, calculations like the above are therefore for illustrative purposes only. In a clinical

setting, blood Hb levels below 1 g/dl for more than a short time is lethal; survival for hours/days with Hb levels between 1 and 2 g/dl has, however, been described in case histories (see Tolerance to Anemia, Part 2-4).

In *anemia*, the reduction of C_aO_2 is *roughly proportional* to the reduction in *Hb*. If the **Hb falls from 15 g/dl to 7.5 g/dl** and all other factors stay normal, the calculated C_aO_2 is

C_aO_2 = [(1.34 mlO_2/g Hb x 75 g Hb/l x 97.5/100)) + (0.225 mlO_2/l/kPa x 13.3)]
= 98 mlO_2/l *(bound)* **+ = 3 mlO_2/l** *(dissolved)*

A total of 101 ml O_2/l blood, *or* about **50% lower** than the normal C_aO_2.

If C.O. stays unchanged at 5 l/min, the **DO_2** is then reduced to 50% of normal. A graph showing the C_aO_2 at different PO_2 values for blood with Hb 15, 10, and 7 g/dl, calculated for conditions in normal arterial blood, is shown in fig. 2-24.

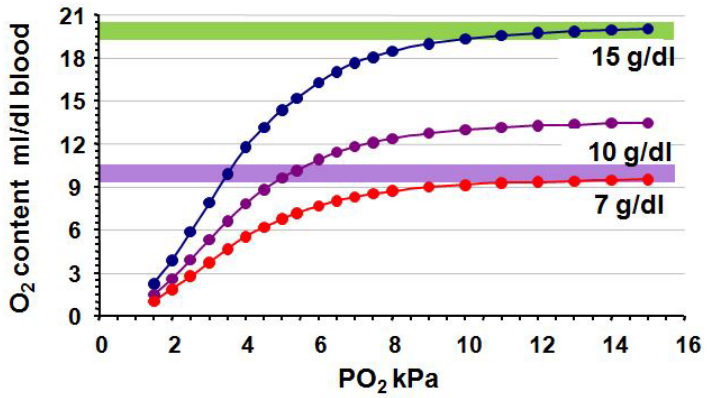

Figure 2-24. *The O_2 content of arterial blood, relative to blood PO_2, for three levels of Hb. A normal HbO_2 curve (pH=7.40) is assumed. The horizontal green bar indicate normal range, the lilac bar a 50% reduction. Note that for all Hb levels, the O_2 content increases only marginally for PO_2 > 8 kPa (60 mmHg).*

An Hb reduction is accompanied by decreased blood viscosity. This reduces the resistance to ejection of the stroke volume, which in most persons increase the C.O. This effect comes *in addition* to any increased inotropic and chronotropic effect on the myocardium produced by sympathetic stimulation and blood catecholamine levels – (see Part 3-1).

If the *PO_2 is reduced* to 6 kPa in a patient with Hb 7.5 g/dl after developing respiratory failure, resulting in a S_aO_2 of 80%, the calculated C_aO_2 becomes

C_aO_2 = [(1.34 mlO_2/g Hb x 7.5 g Hb/l x 80/100)) + (0.225 x mlO_2/l/kPa x 6)]
= 80.4 mlO_2/l *(bound)* **+ = 1.4 mlO_2/l** *(dissolved)*

A total of 81.8 ml O_2/l blood, or close to **40%** of normal.

To maintain an unchanged DO_2 in such a person, a C.O. 2.5 times the normal value (**green**) would be necessary:

DO_2 = **0.4** x (**C_aO_2**) **x 2.5** x (**C.O.**) **= 1**

A graph showing the C.O. that would be necessary for maintaining normal DO_2 (1000 ml/O_2/min) and a 50% reduction at various Hb levels (50% is close to the critical level for maintaining aerobic metabolism at rest, (see Critical DO_2 below) is shown in fig. 2-25.

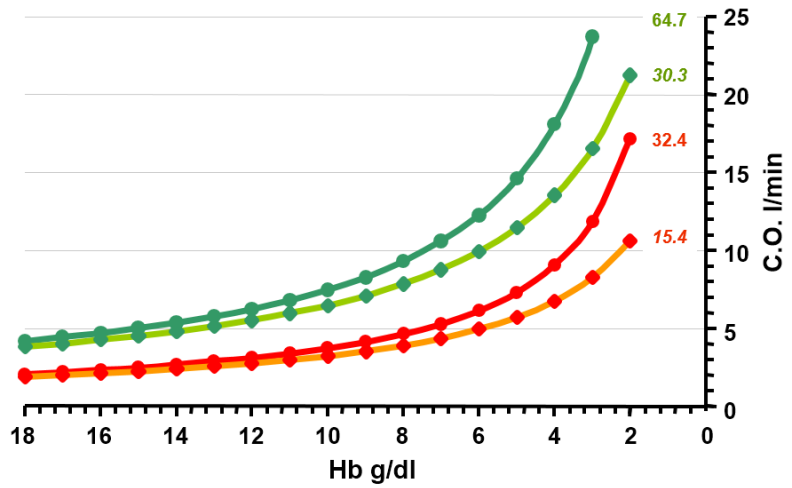

Figure 2-25. *Graphs showing the calculated C.O. necessary to maintain a normal (green) and a 50% reduced (red) level of DO_2 at various values of Hb, assuming a normal HbO_2 curve. Darker colours refer to a normal PO_2 of 13.3 kPa, lighter colours to a PO_2 of 90 kPa (see text). Coloured numbers denote the C.O. needed at an Hb level of 1 g/dl.*

From such calculations, it is easy to recognize that persons with subnormal Hb levels are less tolerant to arterial hypoxemia and that the ability to mount an appropriate C.O. increase is a prerequisite for tolerance to severe anemia. Not all O_2 in the blood can be utilized by the tissues; at maximal extraction, about 8-10% of the O_2 remains bound to Hb when tissue PO_2 falls below critical levels (see HbO_2 curve above). The clinical consequences of anemia, as well as indications for erythrocyte transfusions, are discussed below.

Diminished ratio between O_2 delivery (DO_2) and $\dot{V}O_2$.

DO_2	$\dot{V}O_2$	OE %	S_VO_2%	ΔS_VO_2%
50 % ↓	25 % ↓	38	60	-13
	Normal	50	47	-25
	25 % ↑	63	35	-38
Normal	25 % ↓	19	79	6
	Normal	25	72	0
	25 % ↑	31	66	-6
50 % ↑	25 % ↓	13	85	13
	Normal	17	81	8
	25 % ↑	21	77	4

Table 2-2. *Effects of a 50% reduction or increase in DO_2 from normal on the percentage of oxygen extraction (OE), mixed venous S_VO_2 and change (Δ value) from normal S_VO_2. Green areas indicate normal $\dot{V}O_2$; the effects of simultaneous changes in $\dot{V}O_2$ (25% decrease or increase) are also shown.*

The percentage O_2 extraction from the blood may increase from 20-25% to 70-80% or even more before the PO_2 in microcirculation and tissues is reduced to critical levels. These values represent mean values for the whole body; the ratio between resting O_2 consumption and supply varies considerably between different organs (fig. 2-8). Even if the kidneys consume slightly less than 10% of the supplied O_2 due to the high volume of blood necessary for filtration in the glomeruli (fig. 2-8), the renal *medulla* has a high O_2 extraction (190). The renal medulla is therefore sensitive to severe reductions in perfusion, and renal failure is often seen after periods of circulatory shock.

The first line of defense against tissue hypoxia is to increase the extraction of O_2 from the blood.

Any change in the normal balance between DO_2 and $\dot{V}O_2$ affects the extraction fraction instantly. If the amount of oxygen delivered to the tissues is reduced (e.g. in anemia, circulatory failure, pulmonary failure, carbon monoxide poisoning, etc.) without a similar reduction in consumption,

or the need for oxygen increases (e.g. muscular exertion, fever, hyperthyroidism, high catecholamine levels, burns, stress, post-traumatic phase) without a comparable increase in supply, the ratio between O_2 supply and consumption changes. Such a change in O_2 extraction of the whole organism is reflected by a changed mixed venous SO_2 and the calculated CO_2, as illustrated in table 2-2.

The second line of defense is to increase the cardiac output.

In persons with a healthy heart and adequate preload, a reduced $\mathbf{C_aO_2}$ increases the C.O. which reduces the increase in extraction considerably (191). On the other hand, in situations where the $\dot{V}O_2$ is reduced but DO_2 is maintained, *or* the DO_2 is increased in the face of normal $\dot{V}O_2$, the O_2 extraction from the blood is reduced and the venous SO_2 increases. If changes in $\dot{V}O_2$ are accompanied by a change in DO_2 of equal proportions, however, the venous SO_2 remains unchanged.

Simple bedside estimation of C_aO_2 and DO_2 as fractions of normal values.

Since physically dissolved oxygen usually constitutes only a small proportion of the oxygen content of the blood, approximate bedside calculations patient's O_2 transport status may in most instances be performed *without* taking the PO_2 into account. The CaO_2 can then be calculated as a fraction of "normal values" for each of the factors involved (i.e. Hb 15 g/dl and S_aO_2 97.5%), we can then calculate the deviation from normal values as a product of fractions:

C_aO_2 as a **fraction** of normal values (**in green**): **Patient Hb/15 g/dl** × **Patient S_aO_2/97.5%**

If the patient **Hb = 10 g/dl** and **S_aO_2 = 88%**, the **C_aO_2 as a fraction** of the normal value in green (i.e. ≈ 20 ml/100 ml blood) is:

C_aO_2 fraction: 10/**15** x 88/**97.5** = 0.67 x ca. 0.9 ≈ **0.6 of normal.**

i.e. around **60%** of the normal value.

If the cardiac output is known, the actual DO_2 may also be calculated as a fraction of the normal value. If the patient's body size, temperature, etc. implies a normal resting C.O. of about 5 l/min, and the current C.O. is measured as 4 l/min, the product of fractions, i.e. the **actual DO_2 as a fraction of normal**, is

DO_2 fraction: 10 g/dl/**15 d/dl** x 88/**97.5** x 4/**5** **= 0.48 of normal.**

i.e. the oxygen supply to the body is **slightly below 50%** of that in a resting healthy normal individual and in the *critical range.*

Clinical conditions causing changes in O_2 extraction from the blood.

Any change in the ratio between **$\dot{V}O_2$ and DO_2** leads to a change in the venous SO_2, either locally or in the mixed venous blood. The higher oxygen extraction an organ has under normal conditions, the lesser the capacity to increase the OEF as a "first line of defense" compensatory mechanism when the oxygen supply is reduced. Organs with a high O_2 extraction are therefore more vulnerable than others when oxygen supply is reduced; they have, however, an increased ability to increase their blood flow (autoregulation) when VO_2 increases *or* the C_aO_2 decreases.

A reduced venous S_VO_2 despite a normal C_aO_2 represents a warning that an unfavorable change in the **$\dot{V}O_2/DO_2$** ratio has taken place, but does not identify *which* of the factors has changed. On the other hand, if both factors change by the same fraction, the venous S_VO_2 may stay unchanged.

Low S_vO_2 due to decreased DO_2.

Any reduction in DO_2 (reduced C_aO_2 and/or C.O., see above) without a proportional reduction of $\dot{V}O_2$ causes a fall in venous SVO_2. The clinical conditions most commonly associated with such states are described in Parts 3-3 and 4-3.

Low S_vO_2 due to increased $\dot{V}O_2$ during muscular exertion.

During mild to moderate muscular activity in healthy persons, the percentage increase in cardiac output (C.O.), relative to resting values, is almost linear and amounts to around 40-50% of the percentage increase in $\dot{V}O_2$ (192). At higher $\dot{V}O_2$ rates, the relative rise in C.O. is attenuated; in well-trained athletes, the close to 1:2 ratio of the C.O./$\dot{V}O_2$ increase may remain linear up to a $\dot{V}O_2$ around 4 l/min (48). As the DO_2 is determined by the O_2 content of the blood and the C.O., the O_2 supply to the microcirculation (see below) is reduced relative to the tissue consumption. This is compensated for by an increased O_2 extraction from the blood; consequently, the O_2 content of venous blood is reduced and the difference between arterial and mixed venous blood O_2 (the arterio-venous (a-v) O_2 content) increases in magnitude (48).

During heavy exercise, the metabolic expenditure in healthy athletes may approach 20 times that at rest (49); a 3 to 5-fold increase in C.O., and thus DO_2, during such exercise (48, 49). cannot satisfy the increased O_2 demand (see also Part 3-2). The O_2 extraction increases further, and the SO_2 of mixed venous blood may be reduced to 12-15%. Under such conditions, 85-90% of the circulating blood perfuses exercising muscle tissue while flow to the rest of the organism is reduced by 30-35% (193); the high degree of O_2 extraction measured in the greater veins therefore mainly reflects an even higher extraction in the muscle tissue (194). This is made possible by acidosis in the muscle microcirculation with a pH close to 7.0 (48) or even lower (195), which allows the SO_2 to fall to 12-15% before the critical end-capillary PO_2 of 2.7 kPa (20 mmHg) is reached (see also fig. 2-20). During maximal exercise, the S_vO_2 in the blood draining major muscles may decrease to 8-10% (194), this may represent the lower limit for O_2 extraction in tissues (see also ref 110).

By extracting the maximal amount of O_2 that can be released by the blood, trained athletes may maintain aerobic metabolism up to a level of about 70-80% of maximal effort (48). Above this level, anaerobic metabolism must cover part of the metabolic needs, resulting in increased production of lactic acid and the development of systemic lactacidosis (196, 48).

High S_vO_2 due to increased DO_2 relative to $\dot{V}O_2$, or to reduced $\dot{V}O_2$.

Conditions also exist in which the supply of O_2 is *increased* relative to the consumption; the degree of oxygen extraction is then *lower* than normal and the O_2 content of mixed venous blood is then *higher* than normal (see table 2-2). This applies above all to conditions in which an increase in C.O. is substantially higher than the accompanying increase in O_2 consumption (see below), but may also be due to mitochondrial dysfunction with failure to utilize the supplied O_2 (e.g. mitochondrial dysfunction induced by hypoxia, toxins, certain drugs, inborn errors of function).

High S_vO_2 is seen relatively often in patients who have a high C.O. (a *hyperdynamic circulation*) due to low vascular resistance and inotropic support in well-compensated gram-negative sepsis, but may also occur in patients with liver failure, after stabilization of patients having suffered major trauma, and in other inflammatory conditions (see also Part 3-3). Post-hypoxic reduction in $\dot{V}O_2$ after cardiac arrest may also cause the central venous oxygen saturation to be much

higher than that expected relative to the C.O., provided that the arterial oxygen content is normal. Increased mortality in severely ill patients who have a very high central venous SO_2 has been reported (197, 198, 199), supporting the assumption that both sepsis and severe tissue hypoxia may induce mitochondrial dysfunction and thus reduce the metabolic efficiency.

Elevated S_vO_2 due to cardiac – or vascular shunt.

Elevated S_vO_2 may in rare instances be due to other mechanisms than an increased $DO_2/\dot{V}O_2$ ratio. In persons with large arteriovenous shunts and other central vascular anomalies, SO_2 may be elevated in both central veins and the pulmonary artery despite normal or reduced DO_2 (200). In ventricular septum defects of the heart, with left-to-right shunting (see Part 3-2), blood samples from the pulmonary artery will show an elevated SO_2 despite a severe decrease in blood flow (and thus oxygen supply) to the systemic circulation (201), while the SO_2 in samples obtained from a central vein will be decreased.

The balance between supply and consumption also changes in disease; analysis of the a - v O_2 balance may give important clues as to whether further treatment aiming to secure an increase in DO_2 is necessary*or* whether previous interventions have been successful, and downscaling of fluid infusions and inotropic support should be considered (see also Part 3-4).

Interpretation of changes in S_vO_2 (see also Part 5-4).

Interpretation of the $DO_2/\dot{V}O_2$ ratio based on the S_vO_2 may be difficult (see also table 2-2). Metabolic consequences of diseases and prolonged hypoxia (202, 199) may change the $\dot{V}O_2$ also, the metabolic machinery of the cells may function differently in the acute phase (minutes to a few hours), the early phase (the first hours to days), and the late phase (one *or* a few days to death or recovery) of circulatory shock and serious disease.

Efforts to optimize DO_2 in the acute phase of diseases threatening the tissue O_2 supply may reduce complications and the incidence of organ failure (203, 204). Similar interventions, guided by changes in the S_vO_2, may provide little benefit after hypoxic and/or inflammatory tissue damage to cell function is established and/or the production of signal substances inducing mitochondrial dysfunction or damage has already been induced (205, 206). Toxins that inhibit mitochondrial function, e.g. cyanides and hydrogen sulfide, may result in high venous O_2 content due to the inability to maintain aerobic metabolism. In such settings, widespread anaerobic metabolism leads to increased lactic acid production; a combination of *high S_vO_2 and high lactate levels* in the blood should therefore alert the clinician about the possibility of such intoxications.

TRANSPORT OF CO_2 FROM THE CELLS TO THE LUNGS: THE CO_2 CONTENT OF VENOUS BLOOD

CO_2 and water (H_2O) are the major end products of aerobic metabolism through the citric acid cycle (see previously); the CO_2 gas diffuses rapidly out of the cells, through the interstitial fluid, and into the capillary plasma along a pressure gradient (see also Part 5-2, fig 5-4). The CO_2 gradient between tissue cells and blood is maintained by two mechanisms

- The **conversion** of most of the CO_2 from dissolved gas into bicarbonate and carbamino compounds immediately after entering the erythrocytes (see below) reduces the PCO_2 in the capillary plasma, *and*
- The **convective transport** by the blood flow through the microcirculation removes the CO_2 away from the tissues.

The states of CO_2 in the blood and their relative importance for CO_2 transport.

The CO_2 molecules in the blood are present in three different states (fig. 2-26). The total **CO_2 content of mixed venous blood** (i.e. the *weighted mean* CO_2 content of the blood leaving the microcirculation of various tissues) is, under normal conditions, distributed as (207, 208):

- **CO_2 molecules dissolved as a gas,** representing ≈ **5-6 %** of the total, which corresponds to a mean PCO_2 measured in mixed blood of about 6.1 kPa (46 mmHg).
- **Bicarbonate (HCO_3^-) ions,** representing ≈ **87%** (calculated normal value ≈ 24 mmol/l).
- **Carbamino compounds** (i.e. Hb-bound CO_2), representing ≈ **7 %** (not routinely measured).

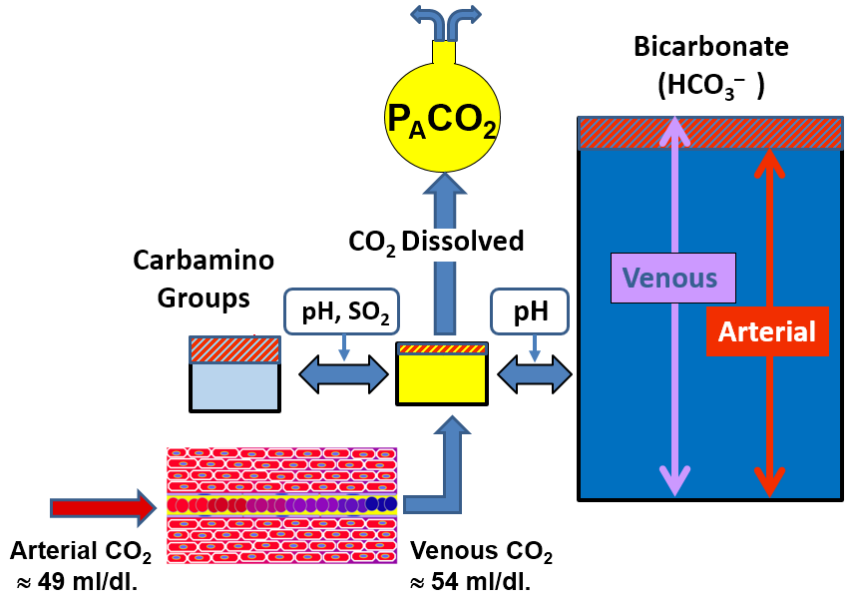

Figure 2-26. *Transport of CO_2 by the blood. The equilibrium between dissolved CO_2 (represented by PCO_2, yellow rectangle), bicarbonate (dark blue rectangle) and carbamino groups (light blue) is determined by the factors shown in the figure. The area of the squares is representative for the normal amounts of CO_2 in mixed venous blood. Hatched areas indicate normal resting difference between venous and arterial blood.*

In arterial blood, the percentage of carbamino compounds is reduced to ≈ 5%; the total CO_2 content is reduced by about 8%. The number of **CO_2** molecules dissolved as a gas (i.e. **PCO_2**) is *always* in equilibrium with the number transported as **HCO_3^-** and **carbamino compounds** (fig 2-27). As the balance between the above states of CO_2 varies with both *blood pH* and the *O_2 saturation of the Hb*, changes in PCO_2 *per se* do not accurately reflect a change in the total amount of CO_2 in the blood when SO_2 and pH also change.

Transport of CO_2 as gas dissolved in the fluid phase of the blood.

CO_2 gas has a high solubility in aquatic media, about 20-24 times that of O_2 (209). At 37°C, approximately 0.5 ml CO_2 is dissolved per dl blood for each kPa pressure of CO_2 gas (or 0.067 ml per mmHg); with a mixed venous PCO_2 of 6.1 kPa, the amount of dissolved CO_2 is about 0.5 ml/kPa/dl x 6.1 kPa = 3.1 ml/dl blood (compared to about 0.3 ml/dl of O_2 in arterial blood at 13.3 kPa). The difference in PCO_2 between mixed venous and arterial blood (ΔPCO_2) at rest reported by most authors is in the 0.5-0.8 kPa (4-6 mmHg) range (210, 211); a value as low as 0.3 kPa (2 mmHg) was reported in one study (212).

Despite the high CO_2 solubility, the amount of molecules that are transported as dissolved gas by the blood *from* the microcirculation *to* the lungs represents only approximately 5-6% of the total CO_2 content of the venous blood. The rest is transported as bicarbonate ions and carbamino compounds (see below).

Transport of CO_2 as bicarbonate ions.

When gaseous CO_2 is dissolved in aquatic fluid, some of the CO_2 molecules become *hydrated*, i.e. they react with water to create carbonic acid (**H_2CO_3**) which dissociates into bicarbonate (**HCO_3^-**) and hydrogen ions (**H^+**) (see also Part 5-2). In most aquatic media of the organism (interstitial fluid, plasma, cerebrospinal fluid), hydration is a slow process at physiological pH values (213). Most of the CO_2, therefore, remain as dissolved gas molecules until they diffuse into the erythrocytes, where the intracellular enzyme *carbonic anhydrase (CA)* makes the reaction virtually instantaneous (see below). The carbonic acid then dissociates into H^+ and HCO_3^- (bicarbonate ions)

$$\mathbf{CO_2 + H_2O} \xrightarrow{CA} \mathbf{H_2CO_3} \rightarrow \mathbf{H^+ + HCO_3^-}$$

The HCO_3^- ions are subsequently transported out of the erythrocytes in exchange for Cl^- ions (the *chloride shift* (214)).

The amount of dissolved CO_2 that is transformed into HCO_3^- depends on

i) the CO_2 tension,
ii) the blood temperature *and*
iii) the intra-erythrocyte acidity (see also Part 5-1).

Transport of CO_2 as carbamino compounds.

When CO_2 molecules diffuse into the erythrocytes, some of them bind directly to the Hb molecules as *carbamino compounds*, i.e. the CO_2 molecules bind reversibly to the NH_2 side group of the amino acid histidine in the Hb molecule. Other proteins may also bind CO_2 as carbamino compounds; their contribution to the total is, however, small. The molecules that have released their O_2 (are *desaturated*) have an increased capacity for forming such compounds; venous blood has thus a slightly higher content of such compounds than arterial blood.

The creation of bicarbonate and carbamino compounds reduces the number of free CO_2 molecules dissolved in the blood and thus maintain the gas pressure gradient between CO_2 in the cells and the microcirculatory plasma. When the blood reaches the lungs and the PCO_2 is reduced as a result of diffusion of the gas from the blood to the alveoli, the direction of the reactions is reversed (see Part 4-1 and Part 5-2).

Relationship between tissue CO_2 generation and blood flow.

The CO_2 content of venous blood draining an area of tissue is determined by the ratio between ***i)*** the total amount of CO_2 generated by aerobic metabolism *and* bicarbonate buffering, see Part 5-2, *and **ii)*** the rate of blood flow through the tissue. In clinical settings, changes in the measured PCO_2 are often assumed to be proportional to changes in blood CO_2 content; this may be inaccurate when the balance between the three states change (see above and ref. 215).

Failure of the microcirculatory blood to remove CO_2 at the same rate as it is generated by the tissue leads to

- A **decreased gas diffusion gradient** between cells and blood, resulting in intracellular accumulation of CO_2, intracellular acidosis, and decreased metabolic efficiency.
- **Increased CO_2 in the venous blood** (a *venous* "respiratory acidosis"); whether this also results in an *arterial* acidosis depends on the pulmonary capacity for excretion of CO_2 (see Part 4-2).

Venous and arterial PCO_2 during high-flow states in the microcirculation.

During *strenuous exercise* in well-trained persons, aerobic and anaerobic metabolism run in parallel (216), both increased aerobic metabolism and bicarbonate rehydration to CO_2 due to local lactacidosis contribute to the increase in CO_2 generation. The blood flow through the muscle microcirculation also increase but CO_2 generation increases considerably more than the blood flow, causing the PCO_2 in mixed venous blood to be more than twice that in arterial blood. In one such exercise study, P_VO_2 was 11.7 kPa (87 mmHg) vs P_aO_2 4.9 kPa (37 mmHg), respectively (48). PCO_2 in veins draining the most active muscle groups can be more than 3 times higher than in arterial blood (e.g. PCO_2 14.3 kPa (107 mmHg) vs 4.7 kPa (35 mmHg)) (217). The *arterial* PCO_2 under such conditions is normal or slightly subnormal, due to the concomitant increase in both ventilation and C.O.

Venous and arterial PCO_2 during low-flow states in the microcirculation.

In *acute low–flow state*s with insufficient O_2 delivery (e.g. during CPR, cardiac or hypovolemic shock), the tissue O_2 consumption becomes supply dependent; below the critical O_2 supply level, reduced aerobic and increased anaerobic metabolism run in parallel. The aerobic CO_2 production is reduced, production of lactic acid, and thus generation of CO_2 from buffering by HCO_3^- (see Part 5-2) increase, however, simultaneously. The total CO_2 production is maintained during the initial phase; with increasing tissue and microcirculatory acidosis the HCO_3^- levels are reduced to very low levels (218) and the buffering capacity decreases.

If the reduction in blood flow is greater than a corresponding reduction in the total CO_2 generation, the PCO_2 in venous blood leaving the tissues (and therefore also in mixed venous blood) increases, analogous to the situation during a strenuous exercise described above. The venous PCO_2, relative to the arterial value, increase in low-flow states; such increase can be considered a rough measure of tissue flow inadequacy. The CO_2 generation during severe tissue hypoxia is difficult to predict, the veno-arterial CO_2 difference can therefore not be used to quantify the reduction in perfusion accurately but may be useful as a qualitative indicator.

Whether the *arterial PCO_2* during the above states is increased or decreased depends on whether the alveolar ventilation increases more than, less than, or matches the change in the total CO_2 generation. Samples of venous and arterial blood can show a different acid-base state in low-flow conditions. A picture of *combined* respiratory and metabolic acidosis in venous blood (high PCO_2 and reduced Base Excess) in samples of mixed venous blood may co-exist with a *pure* metabolic acidosis with partly respiratory compensation in arterial blood (normal or reduced PCO_2 and reduced Base Excess) (see also Part 5-3).

2-4. OXYGENATION FAILURE, ORGAN DYSFUNCTION

Failure of oxygenation - clinical definitions.

Hypoxia is a critical reduction of the tissue cells O_2 supply to a point where aerobic metabolism cannot be sustained in all parts of the tissue. Hypoxia does not necessarily lead to oxygenation failure in *all* the tissue cells; using the Krogh cylinder (fig. 2-27) as a model, the cells situated closest to the arterial end of a capillary may still enjoy a satisfactory blood-to-cell O_2 gradient while the cells located at the venous end and farthest from the capillary must resort to an anaerobic metabolism for energy production.

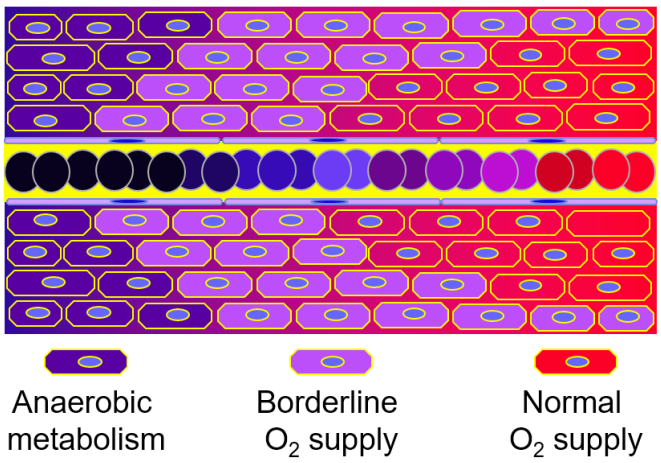

Figure 2-27. *When the blood flow, and thus the capillary-to-cell O_2 gradient, decreases below a critical value, some cells receive borderline amounts of O_2 while those situated most unfavourably may become hypoxic or anoxic.*

Hypoxia must not be confused with **hypoxemia** (see Part 4-2); the latter defines a condition of reduced oxygenation of the arterial blood, i.e. low P_aO_2 and S_aO_2. Grave hypoxemia *may* cause hypoxia, but when hypoxemia is compensated for by an adequate increase in blood flow, the tissue O_2 supply may remain above critical levels and tissue hypoxia will be avoided (see fig 2-25 above).

Anoxia is a state where *no oxygen* reaches the tissues; all cells are deprived of O_2 and will succumb if the O_2 supply is not rapidly re-established (see ischemia-reperfusion below). Tolerance to anoxia and hypoxia (i.e. the time interval before irreversible damage occurs) varies between different tissues; those with the highest metabolic rate are most vulnerable.

Ischemia is a state where grave hypoxia or anoxia is precipitated by *severely reduced or no circulation* to localized areas (or in general). Local ischemia is usually precipitated by vascular occlusion caused by *thromboembolic events or atherosclerotic plaques or* a combination of both; common examples are myocardial infarction and cerebral stroke. Cardiac arrest may be envisioned as a state of generalized ischemia. In addition to the lack of O_2 supply that accompanies ischemia, there is no supply of nutritious substrate and no removal of waste products, limiting the cell's ability to maintain even anaerobic metabolism. Ischemia is therefore the most severe state of O_2 deprivation, with the shortest period before failure of tissue function. As there is little or no venous flow out of an ischemic organ, lactate levels in the circulating blood may show little change in the initial phase of localized ischemia.

Critical O_2 levels for individual cells.

If a decrease in the tissue supply of O_2 is so severe that the microcirculatory PO_2 cannot be maintained above a critical level (see below), the electrons generated by the citric acid cycle will accumulate and the aerobic metabolic process comes to a halt. The anaerobic part of the cell's metabolism continues to function for a short period, during which lactic acid production continues, leading to lactate accumulation in the tissue and subsequent spillover into the microcirculation. As long as there still is flow, the increased lactate can be detected in the venous blood draining the tissue.

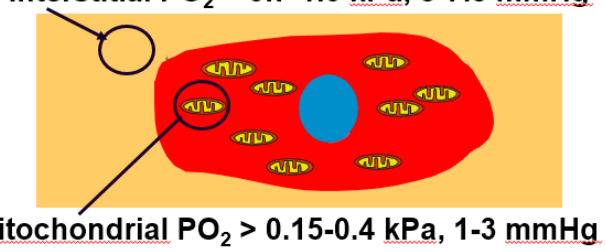

Figure 2-28. *Critical O_2 pressure levels for sustaining aerobic metabolism outside and inside the cells.*

Experimental data indicate that the **PO_2 in the fluid surrounding the cells** (i.e. the **critical PO_2**) must be above **0.7-1 kPa** (5-7.5 mmHg), and the **PO_2 in the fluid surrounding the mitochondria** (i.e. *the intracellular fluid*) must be around **0.15-0.4 kPa** (1-3 mmHg) to maintain an optimal aerobic function (219)(fig. 2-28). In hypothermia, the critical levels are lower (see also fig. 2-21).

Critical end-capillary and venous PO_2.

The lowest venous PO_2 that ensures aerobic metabolism in *all* cells in a tissue drained by a particular vein probably varies between different organs and tissues. Energy requirements, and thus also O_2 demand, change with the temperature and cellular activity of the tissues. The critical PO_2 in veins draining various tissues has been found by various investigators to be approximately 3 kPa (22.5 mmHg) (218), 2.4 kPa (18 mmHg) (220), or even as low as 2 kPa (15.2 mmHg, (221). In this compendium, the value of 2.7 kPa (20 mmHg) suggested by Nunn (222) and employed by several others (223, 224, 225) is, for simplicity and illustrative purposes, used as the critical venous PO_2 value (fig. 2-29). Below this PO_2, anaerobic metabolism can be expected in tissue cells situated most unfavorably relative to the O_2 supply (fig. 2-27), and the content of lactic acid in the venous blood may start to increase. If this occurs, a rightward shift of the HbO_2 dissociation curve in the microcirculatory blood will make more O_2 available to the tissues.

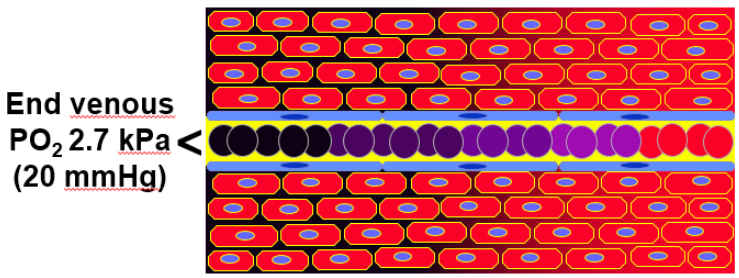

Figure 2-29. *Critical PO_2 in veins draining local tissue areas – see also fig 2-12 and 2-13.*

This PO_2 level in *local end venous blood* draining a specific tissue area must *not* be confused with the critical *mixed venous O_2 content* (mainly determined by Hb and S_VO_2), which represents the weighted mean of the O_2 content of venous drainage from organs and tissues with widely different O_2 consumption relative to perfusion (see above). A *mixed venous* SO_2 < 60% (PO_2 ≈ 5-7 kPa *or* 37-53 mmHg) in patients after cardiac surgery (226), a *central venous* SO_2 < 60% in non-selected ICU patients (227), and *central venous* SO_2 < 70% (PO_2 ≈ 4-6 kPa *or* 30-45 mmHg) during sepsis are all associated with increased mortality.

Critical DO_2 for the organism as a whole.

Any combination of reductions in **Hb**, **S_aO_2**, and **C.O.** can lead to a critically low DO_2. In previously healthy individuals, reductions in Hb are best tolerated; an acute reduction to 1/3 of normal (i.e. around 5 g/dl, see fig 3-20) does not induce signs of tissue hypoxia in healthy volunteers but may represent a borderline level for optimal cerebral function (see below).

Trained mountaineers can, after proper acclimatization, continue to climb even higher with a S_aO_2 in the 50-55% range (125). In such persons, an elevated Hb as a result of acclimatization is common, and probably a prerequisite for continued climbing efforts to be possible. On the other hand, reduction of C.O. by 30% from the normal value is classified as a cardiogenic shock (see Part 3-3).

Regardless of changes in DO_2 and $\dot{V}O_2$, the adequacy of O_2 supply to the cells of each tissue depends on whether or not the necessary O_2 pressure gradient between the microcirculatory blood and the cells is maintained. *For any $\dot{V}O_2$ level, there is a corresponding DO_2 at which the O_2 supply becomes insufficient to maintain aerobic metabolism in some, or most, tissue cells.*

If the DO_2, for any reason, fails to supply the amount of O_2 necessary for maintaining aerobic metabolism in all cells, the baseline $\dot{V}O_2$ decreases and the **$\dot{V}O_2$ becomes supply dependent**. This is the **critical DO_2 level** (also called the "*hypoxic threshold*" or "*lactic acid threshold*") for the whole organism. Below this level, additional reductions in DO_2 cause a proportional further reduction in $\dot{V}O_2$. At variations in DO_2 levels *above* the critical level, the $\dot{V}O_2$ is stable and independent of the DO_2, the $\dot{V}O_2$ is **supply independent** (fig. 2-30). Variations in DO_2 at a constant $\dot{V}O_2$ lead to non-linear changes in mixed venous O_2 content (usually proportional to mixed venous SO_2) and in the arterial-venous O_2 difference, but without a general increase in lactate production.

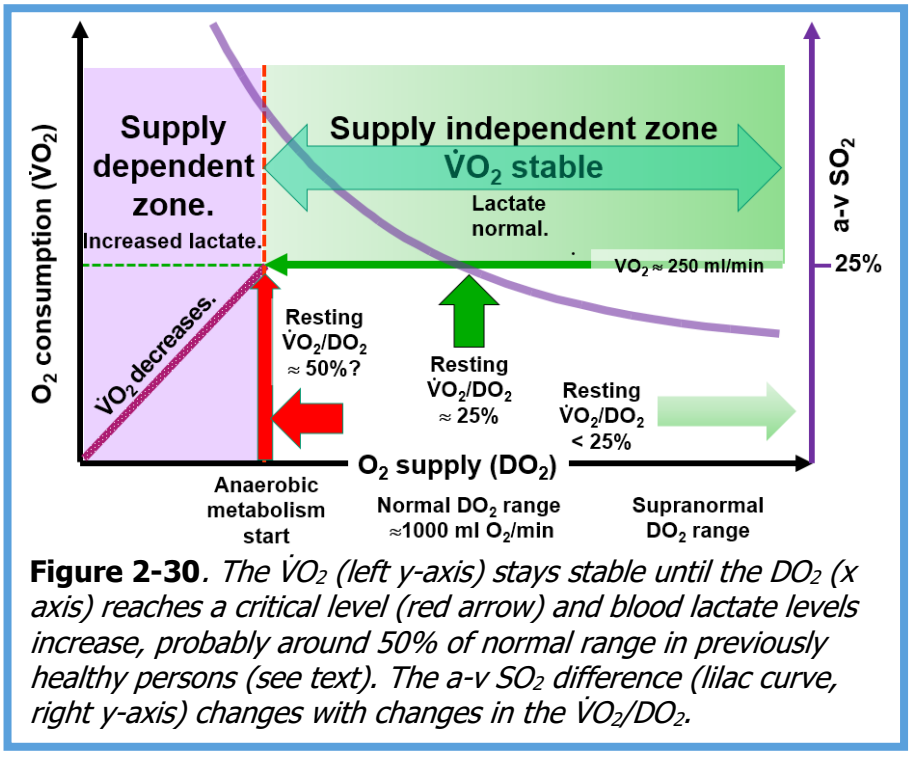

Figure 2-30. *The $\dot{V}O_2$ (left y-axis) stays stable until the DO_2 (x axis) reaches a critical level (red arrow) and blood lactate levels increase, probably around 50% of normal range in previously healthy persons (see text). The a-v SO_2 difference (lilac curve, right y-axis) changes with changes in the $\dot{V}O_2/DO_2$.*

The arterio-venous O_2 content difference increases substantially and the venous O_2 content reaches very low levels *before* the critical DO_2 level is reached (fig. 2-30). The critical a-v difference is somewhere in the 35% to 50% range, depending on the conditions. States with a high a-v difference represent a critical situation; during extreme exertion in athletes, it is usually (but not always) terminated by fatigue before tissue damage occurs. In patients, it cannot exist for long before tissue cells become dysfunctional and subsequently die. Increased cellular lactate production is reflected by a raised lactate level in the venous blood draining a hypoxic tissue. The level in arterial blood, however, increases only if the increased production surpasses the body's ability to metabolize lactate (see previously).

During muscular exertion, a significant increase in lactate levels occurs at about 80% of maximal effort (48); a reduction of DO_2 to about 50% in *resting* healthy volunteers does not increase lactate levels (191). In patients, the critical DO_2 level probably varies with the metabolic changes induced by disease (228); changes in lactate levels also depend on the duration of a $DO_2/\dot{V}O_2$

imbalance. A study of critical DO_2 in dying patients showed a mean critical value around 4 ml/kg (i.e. close to 30% of normal (229)), other studies of anesthetized patients have found the critical value to be around 8 ml/kg (230). In the former study, the mitochondrial function might already be compromised (199), making the critical DO_2 level observed in these patients valid *only* for critically ill patients in the end-stage of disease.

Insufficient O_2 supply: clinical conditions.

Significant reductions in the ability of the microcirculation to satisfy the need for O_2 in the tissues may be due to

- **Reduction in the O_2 content of the arterial blood** (C_aO_2), as caused by hypoxemia and severe anemia (see below).
- **Reduction in global blood flow**, i.e. a decreased C.O. (see below, also Part 3-3), *or* be due to
- **Local changes in the microcirculatory flow**, caused by vascular obstruction/occlusion, compression of vessels by tissue edema, hematomas, etc. It may also be due to pathological constriction of resistance vessels, *or* maldistribution of perfusion, where much of the blood flowing through a tissue flows through only a few, hyper-perfused, vessels.

Conditions affecting microcirculatory oxygen supply to all organs.

Hypoxemia represents a significantly reduced S_aO_2 and P_aO_2, decreasing the amount of O_2 in the arterial blood entering the microcirculation (fig. 2-31). The expression hypoxemia is not well defined; a P_aO_2 < 8 kPa (60 mmHg) or S_aO_2 < 90% are often employed (231, 232), but some investigators have used S_aO_2 levels below 92% (233) or 93% (234) to define hypoxemia (see also Part 4-2). Defining hypoxemia based on the arterial PO_2 *alone* when the value is corrected for the inspired O_2 fraction or pressure, is useful for estimating the gas exchange function of the lungs. The P_aO_2 does not, *per se*, quantify the O_2 content of the blood (see Part 2-3) in persons with Hb within the normal range and is a poor indicator of the DO_2 in many patients.

Anemia, in which P_aO_2 and S_aO_2 may be normal, but the amount of O_2 in the arterial blood is significantly reduced by a decreased number of Hb molecules (fig. 2-25). An important difference between hypoxemia with normal or supernormal Hb (as in most COPD patients) and anemia is, however, that the viscosity of the blood is reduced in the latter. The reduction in resistance to cardiac ejection facilitates an increase in C.O. and thus in microcirculatory flow.

Tolerance to hypoxemia.

Hypoxemia, usually resulting in a reduced C_aO_2, does not necessarily lead to a critical low O_2 supply to the tissues, as increased Hb and/or cardiac output may compensate for even severe reductions in P_aO_2/S_aO_2 (see fig. 2-31). Patients with chronic lung diseases may live with P_aO_2 levels < 8 kPa and a S_aO_2 of 85-90% as a permanent state; most of them have increased Hb levels that compensate in part for the reduced S_aO_2. Many of such patients also have increased pulmonary vascular resistance, as their high Hb also increases blood viscosity, they may have a dysfunctional right ventricle and a limited ability to increase C.O. In well-trained persons with a large cardiovascular reserve capacity and increased Hb levels after acclimatization to low barometric pressures, even extreme hypoxemia (P_aO_2 < 4 kPa, S_aO_2 < 60%) can be tolerated (125) for a limited period.

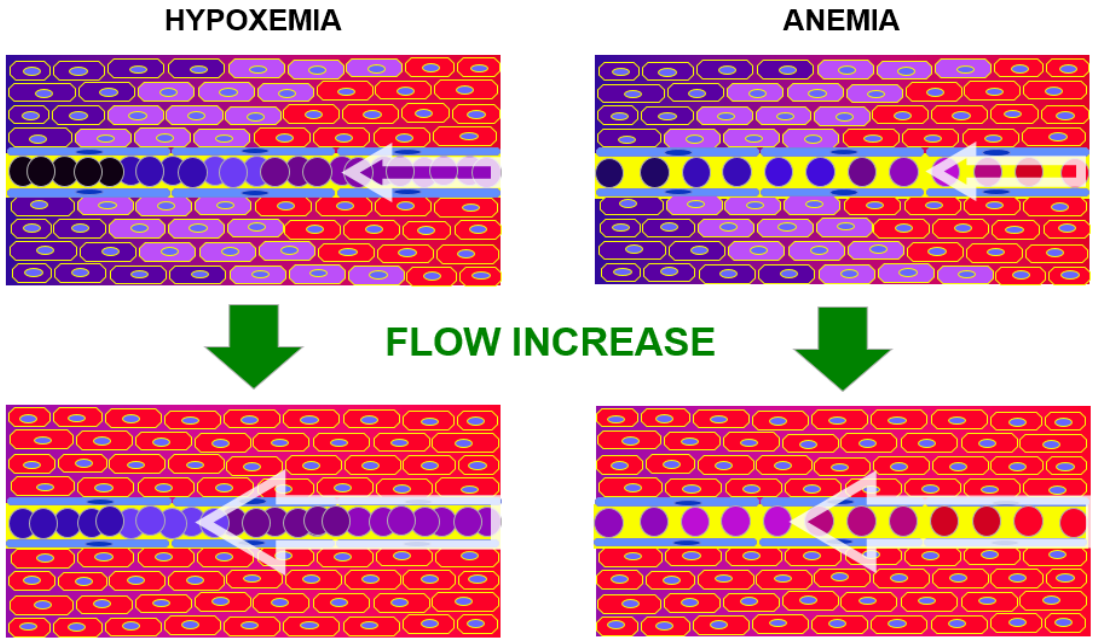

Figure 2-31. *During hypoxemia or anemia that would cause partial tissue hypoxia at normal flow rates, increased flow (i.e. C.O.) can secure oxygenation of all cells.*

During *hypoventilation* , when hypercarbia and respiratory acidosis accompanies hypoxemia, a high P_ACO_2 may have dual negative effects on S_aO_2. If the P_ACO_2 (and P_ACO_2) increases to, or above, 9.5 kPa (71 mmHg) in persons with perfectly normal alveolar-capillary function (see Part 4-1), the corresponding alveolar PO_2 is about 8 kPa (60 mmHg) (see alveolar air equation). Simultaneously, the accompanying respiratory acidosis induces a rightward shift in the HbO_2 dissociation curve (see above), which decrease the S_aO_2 further (from 91% to around 85%).

Tolerance to anemia.

Reduced Hb levels (anemia) are accompanied by an almost equivalent decrease in the O_2 content of the blood; even severe anemia can, however, be compensated for by a combination of increased C.O. and O_2 extraction from the blood. In adults, anemia is classified by the WHO as **mild** if Hb*>11 g/dl,* **moderate** if *11 g/dl* >Hb> *8 g/dl,* and **severe** if Hb*< 8 g/dl* (235).

In clinical medicine, an *Hb of* **10 g/dl** has long been considered sufficient for most patients, and may even represent the optimal value for tissue oxygenation at rest in persons with normal circulatory function (236). In healthy volunteers, an acute reduction of Hb to about **5 g/dl** by removing successive aliquots of blood is well tolerated as long as the lost blood volume is replenished with other fluids and the filling volumes of the ventricles are maintained at normal levels (191). A slight affection of cerebral function can, however, be detected at this Hb level (237).

Based on a large randomized study in severely ill (but circulatory stable) patients (238), an Hb of **7 g/dl** has often been recommended as the lower acceptable level even for intensive care patients. The actual mean Hb of patients in the "low Hb" study group was, however, 8.5 g/dl.

In patients where cardiac dysfunction or disease limits the compensatory increase in C.O., the optimal Hb may be in the 8-10 g/dl range (239); in patients with severe brain injury, Hb < 9 g/dl was associated with increased mortality (240). Thus, the optimal Hb in most severely ill patients

probably lies somewhere between 7 and 10 g/dl; patients with limitations in general or localized perfusion may do better with values closer to 10 g/dl. Even if low Hb levels are associated with increased mortality and morbidity, elective transfusions of erythrocytes to increase the Hb levels (see below) do not necessarily improve the outcome (128, 241).

In parts of the world where both malnutrition and hemolytic diseases (e.g. thalassemia, malaria) are common, chronic Hb values in the 3.5-5 g/dl range are frequently seen (242); when such anemia develops over time, it seems to be well tolerated. In two young patients presenting with previously undiagnosed hematologic malignancies, a Hb of around 2 g/dl was compatible not only with survival but with walking without support (243).

There are, however, well documented case reports of survival without major sequelae after prolonged extreme anemia due to acute hemorrhage: Hb of 1.8 g/dl (244) and even 1.4 g/dl have been tolerated for hours to days (245, 246). Survival with even lower values can be tolerated for a limited period. Patients in which Hb decreased to 1.1 g/dl (247) and 0.7 g/dl (248) due to acute intraoperative bleeding and delays in transfusion have been reported to survive without major sequelae.

Indications for blood transfusions.

Blood transfusions in modern western medicine carry a very small risk of infections and hemolysis. In addition, immunologic reactions may in rare instances lead to acute pulmonary dysfunction which may compromise the oxygenation of the blood (Transfusion Related Acute Lung Injury – TRALI (249)). The decision to transfuse erythrocytes should not be based on the goal of normalizing the Hb levels, but to ensure an Hb level compatible with adequate O_2 tissue supply in each patient. The benefits of transfusing fresh vs stored blood have been discussed by many authors (250, 251), a recent review could not, however, find good evidence for the superiority of either of the strategies (252).

Based on the results of the multicenter study cited above (238), a transfusion trigger of 7 g/dl has been advocated even for severely ill patients. It is important to realize, however, that patients included in that study were judged to be euvolemic and circulatory stable, and could thus be assumed to mount an appropriate cardiac response to reduced Hb levels. Guidelines from a German expert group have suggested an even lower transfusion trigger of Hb 6 g/dl in patients without co-morbidities and signs of cardiac hypoxia (253). Recent guidelines from the United Kingdom suggest a trigger of Hb 7 g/dl with a treatment goal of 7-9 g/dl for most patients, but a trigger of Hb 8 g/dl and a treatment goal of 8-10 g/dl for cardiac patients comment, however, that the suggestions are based on low-quality evidence.

The assumption that an Hb of 7 g/dl is sufficient may not hold true in acute settings. In surgical patients, various co-morbidities and underlying diseases complicate the situation. In patients with Hb 8.0-7.1 g/dl, the outcome after elective surgery showed no significant increase in mortality, but increased morbidity (255). A decrease in Hb below this point increased also the mortality. Another retrospective study of surgical patients detected an increased risk already at an Hb of 10 g/dl for patients with pre-existing cardiovascular disease (256). In a recent analysis of the benefits of using 8 g/dl or 10 g/dl as a transfusion goal for hospitalized patients, no difference was found (257).

In trauma with massive hemorrhage, the circulatory state of patients may be extremely difficult to assess during the initial phase; a transfusion trigger of Hb 7 g/dl in such patients before control of bleeding has been accomplished and cardiac diastolic filling is secured may lead to tissue hypoxia. In acute sickle cell crisis, transfusion (to an Hb of 8 -10 g/dl or higher) may be indicated (258). Whether or not to transfuse depends on the oxygenation problem of the individual patients, and should therefore be tailored to each patient's known or assumed needs.

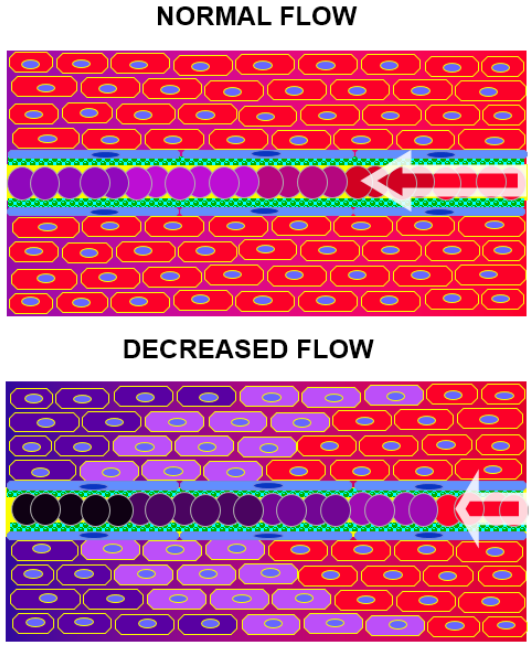

Figure 2-32. *Hypoxia due to decreased flow cannot be compensated for.*

Low flow states. In both hypoxemia and anemia, an increased flow may compensate for the reduced O_2 content of the blood (fig. 2-31). If the tissue oxygenation problem is created by low flow (fig. 2-32), neither increasing the Hb (which increases viscosity and impedes microcirculatory flow) nor the PO_2 (which increases the C_aO_2 substantially only if the S_aO_2 is already subnormal) can be expected to compensate for the flow reduction.

Importance of local perfusion conditions.

If the resistance (R) of the vascular bed increases, the blood flow (Q) can remain constant only if the perfusion pressure (P) increases by the same fraction as the increase in resistance (see above). When local increases in vascular resistance in a particular tissue are suspected, as a result of stenosis, vasospasm, or tissue compression (e.g. cerebral edema or hematomas, edema after medulla damage, compartment syndromes), arterial pressure reduction must be avoided if the threatened areas of tissue are to receive an adequate blood flow (fig. 2-33).

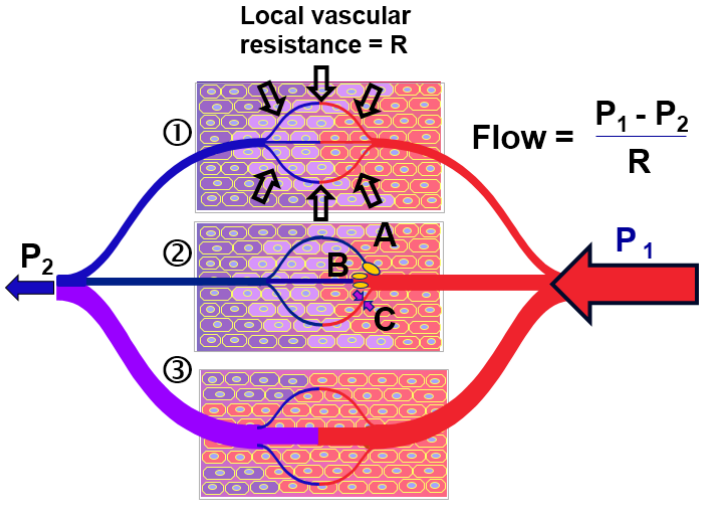

Figure 2-33. *Tissue perfusion may be reduced or abolished by* ① *increased tissue pressure or* ② *occlusion* (**A**), *local stenosis* (**B**), *and vasospasm* (**C**). *Pathological local reduction in local vascular resistance* ③ *may "steal" perfusion from other tissue areas, leaving them hypoperfused. The O_2 content of venous blood draining such tissues may be high, despite areas of hypoxia.*

In certain conditions (e.g. septic shock) there may also be changes in capillary function, so that blood flow in many capillaries will be suspended, and most of the blood will instead flow rapidly through a few capillaries only (228, 259).

In tissue exposed to embolization, thrombosis, infarction, or direct trauma, many cells will sooner or later suffer irreversible hypoxic damage. However, there is often a border zone of *reduced* perfusion around the zone of destruction. In this zone, the cells may be dysfunctional or damaged, but may still have the capacity to regain normal function if optimal perfusion conditions can be re-established within a few minutes to a few hours, depending on the O_2 requirement of the tissue. Under such conditions, the perfusion pressure (i.e. arterial pressure) must also be maintained at a high normal level to ensure perfusion of the border zones until re-perfusion can be established.

Consequences of tissue hypoxia/anoxia.

In isolated cardiomyocytes, metabolic dysfunction can be detected after only a few seconds of anoxia, followed by loss of contraction (260). For a period of many minutes afterward, the cardiomyocytes remain dysfunctional but can regain normal function if reoxygenation is established within 15-20 minutes (261). Beating isolated cardiomyocytes can tolerate up to 45 min, but not 90 minutes of ischemia (262), on the other hand, intact beating hearts made ischemic develop signs of hypoxia within 10-20 sec and may cease to contract within 60 seconds. In experimental models of global cardiac ischemia, all contraction ceases within 10-20 minutes (263). The cells of the cerebrum tolerate hypoxia/anoxia less well than any others; in humans, the cells become severely dysfunctional (i.e. loss of consciousness) within 10 seconds after the arrest of the cerebral circulation (264). They are therefore entirely dependent on a continuous oxygen supply that ensures that the metabolism of the cerebral mitochondria functions normally. In other types of tissue, in which the cells have lower energy requirements (skin, resting skeletal muscle), it will take longer (many minutes or hours) before cell damage and cell death occurs.

In severe circulatory failure (see Part 3-3), the aerobic metabolism of some or all cells will cease to function. When this happens, the cells will, for a limited time, be able to obtain some energy in the same way as the primitive cells referred to above, i.e. by anaerobic (and low-energy yield) metabolism only. The cells rapidly consume the nutrients that are available intracellularly and in the interstitial fluid; as they are also unable to get rid of all of the waste products (e.g. lactic acid) of anaerobic metabolism, the anaerobic metabolism, therefore, functions for only a brief period.

When energy production is reduced, the cells become dysfunctional and are no longer able to perform their specialized functions. They can nevertheless stay alive for as long as energy production is above a minimum threshold. Below this threshold, cell damage takes place. The damage can be repaired, and the cells can survive, provided that normal nutrient and oxygen supply is rapidly restored. Dramatic examples of this include thrombolysis treatments and acute PTCA shortly after myocardial infarction, in which the size of the myocardial infarction can be significantly reduced (265, 266, 267); see also reperfusion injury below.

If, however, the nutrient and O_2 supply cannot be restored within a reasonable period, the damage becomes irreversible and the cells die. Hypoxic injury may also incite an inflammatory reaction that changes the function of the cell in tissues not involved in the primary hypoxic insult (see below).

Reperfusion (reoxygenation) tissue injury.

All cells dependent on aerobic metabolism ultimately die when exposed to hypoxia/anoxia for an extended period. In experimental studies where blood flow to an organ is blocked, the tissue structure of an ischemic organ remains relatively normal microscopically for many minutes-hours.

When perfusion, and thus oxygen, again becomes available (reperfusion), visual signs of tissue damage occur rapidly. This type of damage is called *reperfusion injury* and may be seen as a combination of *post-hypoxic inflammation* and *oxygen toxicity*.

Insufficient blood flow may be due to local changes in the vessels, or general hypoperfusion due to shock. The enzymes in the respiratory chain may be damaged as a result of ischemia, so their capacity to convert O_2 directly to H_2O is reduced and result in increased ROS production and leakage to the rest of the cell. When oxygen again becomes available to the mitochondria, increased quantities of ROS are then formed and leak into the surroundings. This in turn exacerbates the tissue damage, with subsequent tissue and endothelium edema which further reduces circulation in the tissue (268, 269). Such findings constitute an argument against administration of a F_iO_2 higher than necessary to obtain a normal S_aO_2 after an episode of severe hypoxia.

Another source of increased production of ROS under such circumstances is reactions catalyzed by the enzyme xanthine oxidase. This enzyme is created in large quantities in the endothelial cells during ischemia. When the O_2 supply normalizes, this enzyme will use hypoxanthine (a breakdown product of ATP) as substrate and at the same time release the reactive O_2 compounds superoxide (O_2^-) and hydrogen peroxide (H_2O_2)(270).

Protective effect of hypothermia.

Since the metabolic rate (i.e. O_2 consumption) falls when the cell temperature drops (see above), cooling of the tissues reduce their energy requirement and can prevent or ameliorate cell damage during periods of reduced or arrested O_2 supply. Hypothermia may also reduce the inflammation created by ischemia-reperfusion episodes. The most dramatic example of such protective effects is the accidental hypothermia combined with cardiac arrest during drowning in ice-cold water, where rapid cooling of the body and especially the brain occurs. Cardiac arrest during 40 mins submersion in ice-cold water and a rectal temp of 24°C on arrival at the hospital has been reported to be compatible with full recovery (271). Survival with a good outcome after ice-cold water drowning accidents, where body temperatures were even 10°C lower (13-14°C and with prolonged cardiac arrest before warming utilizing extracorporeal devices), have also been reported (272, 273). The lower limit for cooling with survival in humans is not known; organs for transplantation (e.g. hearts, kidneys, livers) perfused with an artificial solution at 5-10°C seem to do better than non-perfused organs cooled with ice (274). In experimental hypothermia studies utilizing dogs, a body temperature of 3°C was the absolute lower limit for survival (275). Certain hibernating animals may, however, tolerate temperatures below freezing (1).

This protective effect has been exploited during deliberate circulatory arrest in connection with certain types of operations on the heart and major vessels. In such instances, the organism is cooled in advance to minimize the potential danger of anoxic damage. Cooling down to body temperatures of 18°C (276), and, in some instances, even 12°C (277) have been used (see also Part 2-3). The effects of hypothermia other than $\dot{V}O_2$ reduction are mostly negative (e.g. hypotension, coagulopathy, suppression of the immune system (278)), limiting its use for prolonged periods.

Mild to moderate hypothermia down to 32-35° C during the first 1-2 days *after* successful resuscitation from cardiac arrest has been assumed to reduce cerebral damage (38, 279), and became part of the post-arrest therapeutic regime (37, 280). The benefits of such treatment have, how-

ever, been questioned (281). The most important effect of a cooling regime may lie in the avoidance of supernormal temperatures; the critical time window for achieving hypothermia is still not been defined precisely (282).

Hypothermia after traumatic brain injury has been investigated by several groups; some find that cooling to around 33° C does not seem to benefit patients with traumatic brain injury and intracranial hypertension (283) while others, based on meta-analyses, conclude with a positive effect in adults but not in children (284).

Cooling the body to *avoid supernormal* temperatures and increased metabolic rate is, however, important in all situations where O_2 delivery to the tissues becomes critical; such therapy has no time limits if a normal body temperature is the target.

Detection of tissue hypoxia

Techniques for monitoring the oxygen supply to the body as a whole are well developed (see Part 3-4). A supply of oxygen that normally satisfies the body's general requirements does not necessarily ensure that the needs of *all* local tissue areas are met; also, interventions that normalize macro-circulatory parameters do not necessary normalize the conditions in the microcirculation (285). In addition, certain diseases, toxic agents, and drugs may inhibit the ability of the cells to utilize the supplied O_2 (see below). In clinical medicine, some devices can measure blood flow and oxygenation in certain locations (286); there are, however, still limited options for continuous bedside monitoring of blood flow and oxygenation within most organs. On the other hand, microcirculatory changes measured by such methods were not found to be strongly linked to survival in a mixed population of critically ill patients (287).

In most organs, acute ischemia (e.g. in myocardial infarction, mesenteric thrombosis, muscle hypoxia) will cause considerable pain. This may be difficult to detect in comatose, anesthetized, or heavily sedated patients, where pain may elicit only non-specific symptoms from the autonomous nervous system. The diagnosis may be further complicated if other known causes of pain exist. Blood lactate measurements are often useful but may not be precise indicators of local tissue hypoxia/anoxia (see below). Threatening hypoxic damage with formation of lactic acid within a restricted tissue area will not necessarily cause a general acidosis or lactate elevation in standard blood samples; as long as other organs with the ability to metabolize lactate (see below) still function normally, the organism as a whole can cope with a moderate increase in lactic acid production. Lactate increases in the blood may also have *other* causes than insufficient O_2 supply (see below).

In some organs, tissue hypoxia are easily detected. Sudden loss of consciousness in a circulatory unstable patient can be assumed to represent cerebral hypoxia, hypoxia in other organs are, however, more difficult to diagnose. Better diagnostic techniques for the monitoring of oxygenation within individual organs and tissue are constantly being developed, and to a certain extent made use of at the bedside. Advanced and automated analysis of ECG recording can give almost instantaneous warning of myocardial ischemia; microdialysis techniques may give early signals of changes in tissue metabolism, and flow both through the microcirculation and larger vessels can be estimated using non-invasive techniques. Even if monitoring techniques are steadily becoming more sophisticated, most methods available to clinicians at the bedside or as laboratory investigations today, (e.g. CT and MR scans, analyses of biochemical markers like troponin, myoglobin, and CK) only confirm that some sort of circulatory derangement and tissue damage has already taken place.

Lactic acid: an ambiguous indicator of tissue oxygenation failure.

A considerable quantity (1500 mmol/day) of lactic acid is produced in the body; under normal circumstances, the same amount is metabolized. Details of human lactic acid metabolism have been reviewed by several authors (224, 288, 289, 290, 291). Some organs have, under normal circumstances, a great capacity to metabolize lactic acid and thereby remove it from the blood. First and foremost the *liver*, but also the *kidneys*, *skeletal* and *cardiac muscle* can utilize substantial amounts of lactate in their metabolism; skeletal muscle consumes much more lactate during moderate activity than at rest (see below). The liver and kidneys also use lactate for gluconeogenesis. As long as these organs maintain their capacity for lactate metabolism, the balance between normal lactic acid production and its elimination results in blood lactate levels in the 0.5 – 1.0 mmol/L range. Almost all of the lactic acid in the blood is dissociated, making the concentration of lactate almost identical to lactic acid – see Part 5-1). A moderate increase in lactic acid production in one or a few organ areas may therefore not result in lactic acidosis in the blood; *a rise in lactate in the arterial blood does not occur until the body's total production of lactic acid exceeds the capacity to remove it*.

Elevated lactate levels can be due to either

- Substantial **increases in the production** of lactic acid.
- Substantial **reduction in the elimination** *or, as in some serious diseases,*
- A **combination of both**.

What levels that should be considered as elevated depends in part on the analytical methods and patient groups; many investigators consider lactate levels equal to, or above, 2-4 mmol/l as elevated and useful as a prognostic tool, especially in sepsis (292, 293, 294).

In strenuous physical exercise, the peak capacity for muscular work is higher than that corresponding to the maximum O_2 consumption of the organism, the $\dot{V}O_{2max}$. The energy for work above the aerobic capacity must be covered by anaerobic metabolism, in which the main mechanism is the anaerobic conversion of glucose to lactate (glycolysis) (49). Lactate accumulation can thus be a physiologic result of massive muscular exertion, or intense muscle contractions, in healthy persons. Lactate levels in the 10-20 mmol/l range can be found in patients after epileptic grand mal seizures (50); in trained athletes exerting themselves to exhaustion, levels up to 30 mmol/l have been observed (195). Such acidosis gradually subside during 1-2 hours after termination of exertion (295); elimination is enhanced by sub-maximal muscle activity after termination of the maximal exertion (296).

In clinical medicine, lactate levels in the blood have been used as a marker of the severity of circulatory failure in critically ill patients. In conditions leading to generalized tissue hypoxia (e.g. circulatory shock, cardiac arrest), the association between lactacidosis and the degree of tissue hypoxia/anoxia is both logical and well documented. The duration of lactacidosis due to short-term, widespread hypoxia in previously healthy persons is usually limited to a few hours if the underlying cause can be rapidly remedied (124).

Even if the oxygen supply is adequate, intoxications (cyanide, hydrogen sulfide), drugs (e.g. biguanides, drugs used in cancer and HIV treatment), and diseases where the mitochondrial function is inhibited, may cause lactacidosis. Also, increased glycolysis, which can be induced by a massive catecholamine stimulation (mostly a β_2 adrenergic effect) may increase lactate levels when the rate of glycolysis increase *more* than the rate of reactions within the citric acid cycle (297).

As lactacidosis may be caused by conditions other than tissue hypoxia, it is often divided into two main classes (298), as initially proposed by Woods and Cohen (299)
Type A, which is caused by *tissue hypoxia, regardless of etiology*, *and*
Type B, with subclasses

- **B1:** Caused by *other underlying diseases* (including reduced elimination)
- **B2:** Caused by *toxins and drugs* (cyanide, biguanides, cocaine, etc.)
- **B3:** Caused by *inborn mitochondrial defects*, e.g. MELAS (300).

In malnutrition and starvation, **thiamine deficiency** may precipitate lactacidosis, especially during the re-feeding phase (301, 302, 303). This is probably an underdiagnosed cause (304) and should be considered when other obvious causes of lactacidosis can be ruled out.

A continuously increased blood lactate level above 4-5 mmol/l, or even lower, has been found associated with increased mortality in patients with circulatory failure, especially when due to severe sepsis (305, 306, 307). It was previously assumed that increased lactate levels in patients with a macrocirculatory adequate DO_2 were due to perfusion defects in the microcirculation (308, 309). In studies of oxygen tension in tissues of septic patients, however, there was no indication of local tissue hypoxia (310); defects in critical enzymes involved in the function of the citric acid cycle, possibly compounded by increased glycolysis, may be the culprit.

The cause of lactacidosis in septic patients may thus be some degree of mitochondrial dysfunction, analogous to the mitochondrial effect of toxins. In severely ill patients, those who show decreased lactate levels after goal-oriented therapy aimed at optimizing the oxygen supply to the body have a much better prognosis than those in which the levels stay increased. One possible explanation could be that in the latter group, mitochondrial damage may already be established. This could also be a logical explanation for why optimizing the oxygen delivery in the very early phase of disease seem to have a beneficial effect (311, 312), while doing the same thing in patients who already require ICU care fails to improve patient outcome (313).

In patients, the absolute level of blood lactate at a given moment is a good predictor of the severity of the disease in individual patients. As a single parameter, however, it is not a good indicator of tissue O_2 supply and does not *alone* indicate a need for aggressive therapy to increase the DO_2 in all patients. Failure to metabolize lactate (and lower the blood levels) after interventions intended to normalize tissue O_2 supply carries, however, a grave prognosis; on the other hand, a reduction in blood lactate during the first phase of resuscitation after the start of treatment may indicate a good prognosis, but not in *all* patients (314).

Interaction between hypoxia and inflammatory processes as a cause of tissue damage.

Many human beings are affected by *chronic* inflammation in individual organs or by general dissemination (rheumatic complaints, autoimmune diseases). *Acute inflammatory processes* play an important role in the development of organ failure in severe disease; the most common causes in emergency and intensive care medicine are *infections, shock, traumatic injuries and burns*, (315, 316, 317). The tissue damage that occurs following severe hypoxia, *reperfusion injury* (see above), may also trigger such processes. Common to all such inflammatory processes is the development of increased microvascular permeability (fig 2-34).

The full details of how inflammatory processes are activated and how they affect the various tissues and organs are not known; the number of pro-inflammatory molecules (e.g. tumor necrosis factor α (TNF α), interleukin 1β (IL-1 β), interleukin 6 (IL-6), and interleukin 8 (IL-8),

reactive oxygen species (ROS), platelet-activating factor (PAF)) that may participate in increasing the capillary permeability is substantial and their numbers are increasing. However, there are good reasons to believe that circulating leucocytes, above all the neutrophil granulocytes (also called polymorphonuclear neutrophils or PMN) play a central role during the first part of the injury process (318, 319, 320). The granulocytes are professional killer cells that are found in large quantities in the blood and can produce a range of substances damaging to tissue (including ROS, see above and Part 4-3, ARDS) when activated. Such activation may be the result of an interplay between signal molecules that activate circulating PMN directly, and/or PMN activation as a result of changes on the surface of endothelial cells.

Several types of signal molecules (mostly pro-inflammatory agents) may affect the function of both PMN and endothelial cells simultaneously. Initial activation of PMN makes them adhere more tightly to the endothelial cells, and if the surface of these are also activated, the process becomes irreversible and the PMN discharge substances that damage the vessel wall. Some signal molecules (chemotactic agents) which are released from damaged tissue or bacteria outside the vessels induce the PMN to migrate out of the vessels, where they continue to discharge their toxic products into the tissue, with further damage as a result.

Several aspects of the endothelial cell surface change character when affected by various signal molecules. Surface molecules in the glycocalyx that inhibits activation of the coagulation system and allows the granulocytes free passage are superseded by molecules that promote coagulation- and attract and activate granulocytes. Such changes in the endothelium also activate platelets, which also play an important part in the inflammatory process. The combination of platelet activation and direct activation of the coagulation system (via tissue factor) leads to thrombus formation in the microcirculation (*micro thrombosis*); activation of elements of both the coagulation system and the immune system reinforce each other in a vicious circle.

Activation of both PMN and the endothelial cell surface may be induced by signal molecules from circulating cascade systems (e.g. the complement system), or lipids like PAF (platelet-activating factor) and products of arachidonic acid metabolism (prostaglandins, leukotrienes, and thromboxane) (321). Other substances are synthesized, primarily (but not only), by macrophages and monocytes. These cells may produce large quantities of proinflammatory cytokines when stimulated; TNF α, IL-1 β, IL-6, and IL-8 are some of the presumably important factors in this context (322).

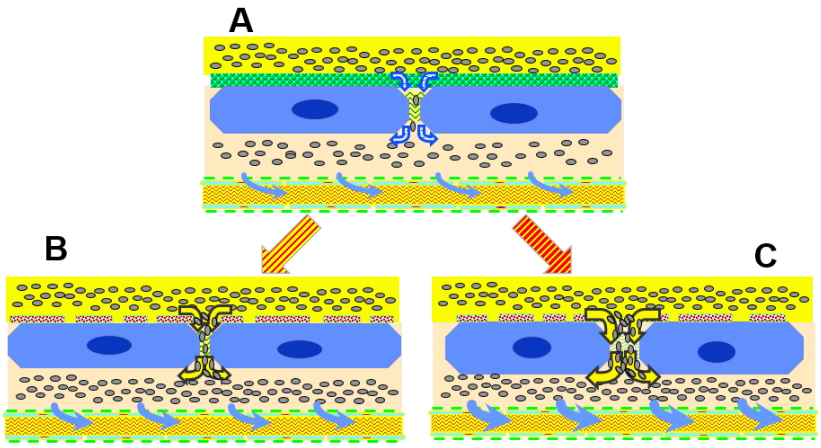

Figure 2-34. A. *Due to the effect of the glycocalyx, the colloid osmotic forces outside the capillary endothelial layer have little effect under normal conditions. Inflammatory changes that damages or disrupts the glycocalyx* **(B)** *greatly increase flux of both water and proteins out of the capillaries. If endothelial cell contraction also occurs* **(C)** (*e.g. anaphylactic reactions), the flux increases further and hypovolemia may occur rapidly.*

This activation of cytokine production may be due to bacterial toxin effects, as in infections and sepsis. Activation may also occur when the cells are affected

by signal molecules released from tissue damaged by trauma (323) or hypoxia (324) or from fractured bone (325). The balance between various pro-and anti-inflammatory cytokines and arachidonic acid metabolites may be important determinants for the aggressiveness of the inflammatory reaction (326).

Irrespective of whether injuries, infections, hypoxic damage, or other external effects initiate the inflammatory processes, it would appear that they act through a variety of pathways but end up generating similar clinical pictures in the end. A systemic inflammatory syndrome **SIRS** (see above) is therefore just as likely to occur as a result of major tissue trauma or hypoxia as of sepsis; the aggressiveness of the SIRS response varies, however, between both etiologies and with individual factors (327, 328). Also, we may be genetically "pre-programmed" as to the response of each individual organism to damaging and pro-inflammatory stimuli, as illustrated by investigations showing a substantial variation in the response of leukocytes exposed to lipopolysaccharide and an association with pulmonary reactivity (329).

Multi-organ dysfunction and failure

Changes in organ function are often seen as a natural reaction to disease and injury, which again are associated with increased levels of proinflammatory cytokines in circulating blood (see above). Activation of the coagulation system and changes in the synthesis pattern of the liver to favor the production of acute-phase proteins (e.g. CRP - C-reactive protein, fibrinogen) are examples of such changes. These are not necessarily negative signs, but may be seen as a natural response to infection or tissue damage. Laboratory signs of consumption coagulopathy with low platelet levels and an increased quantity of fibrin degradation products in the blood are commonly seen in multiple trauma patients, as are increased CRP and reduced albumin production.

The boundaries between *functional changes*, *dysfunction,* and *failure of organs* may be fluid in many contexts. For example, markedly elevated bilirubin is often seen combined with only moderate elevation of liver enzymes and maintained synthesis function in sepsis patients; these changes almost always recede if the underlying condition comes under control.

In *organ failure,* the organ or organ system can no longer maintain satisfactory function, and *replacement* of their function (e.g. dialysis) or *supportive therapy* (e.g. O_2 and ventilatory support) may be necessary to avoid that the failure of one organ lead to further damage to the rest of the organism.

Organ failure may occur as a direct consequence of acute tissue hypoxia that causes cell death. In such cases, the function of the organ starts to fail in seconds or minutes; laboratory evidence may, however, be delayed for many minutes or even hours. Organ failure that arises secondary to inflammatory changes induced by the primary disease or damage develops during the course of hours to days. Renal failure that is due to the toxic effects of the body's endogenous substances (e.g. free myoglobin that causes kidney damage) or exogenous substances (e.g. antibiotics in the aminoglycoside group, x-ray contrast agents) also manifests itself in the course of hours to days.

When many organs fail simultaneously, the condition is termed *multiorgan failure*. The microcirculatory changes that result in this type of organ failure are presumably caused by complex processes in which the effects of hypoxia, reperfusion, microthrombosis, and inflammatory processes reinforce each other and create a vicious circle (270, 330, 331). The capacity of the body to repair such damage (apart from in the CNS) is great, and many types of acute organ failure (ARDS, acute renal failure) may prove reversible if the underlying pathological process responds

satisfactorily to treatment. The reversibility of an organ insult depends on the magnitude and duration of the insult; a state of dysfunction that may be reversible during the early phase of the insult may become irreversible and thus non-responsive to therapy in a later phase. This may be one important reason why therapeutic interventions that are beneficial in the early stages prove to be without effect, or even detrimental, at a later stage (see also above).

Mortality in seriously ill persons increases as the number of failed organs increases (332, 333), i.e. when the sum of problems that *independently* are potentially reversible, becomes too great. When three or more organs fail, and organ function does not improve within a week, mortality has been reported as high as 100%; improvement of organ function during the first 1-2 days seems to be a crucial prognostic factor (334). The aggressiveness of the disease process, or the response to trauma or hypoxia in general, is presumably greater as more organ systems fail. The "sum of problems" may therefore be considered to reflect the aggressiveness of the disease process, and the degree of disruption of the balance between destructive and healing processes.

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PART 3. THE CARDIO – CIRCULATORY SYSTEM

GENERAL INTRODUCTION.

The heart and the macrocirculation are in charge of securing adequate blood flow in the tissue microcirculation. The volume of oxygenated blood flowing from the heart into the systemic circulation, the left ventricular cardiac output (**C.O.**), is a crucial factor for maintaining global aerobic metabolism. Simplified, the main task of the right ventricle (**RV**) is to supply the left ventricle (**LV**) with a sufficient volume of oxygenated blood; while that of the LV is to propel the oxygenated blood onto the rest of the organism. The arterial part of the vascular system distributes the flow between and within the various organs and modifies the distribution in accordance with changes in tissue metabolism and O_2 consumption.

Role of the circulation in maintaining oxygen transport.

As the right and left sides of the heart work in series (fig. 3-1), the LV cannot pump more than what the RV supplies, which makes also the RV function crucial for the C.O. Together with the O_2 content of the arterial blood (the $\mathbf{C_aO_2}$), the C.O. determines the O_2 delivery to the organism ($\mathbf{DO_2}$, Part 2-3). Reductions of the C_aO_2 may be compensated for by increases in C.O., the C_aO_2 becomes, however, irrelevant if there is little or no perfusion of the tissues.

Changes in arterial blood pressure (**ABP**) are often associated with changes in C.O. The ABP has, *per se*, no impact on the DO_2 but are important for the local perfusion pressure, and thus the microcirculatory flow through the tissues. Given constant vascular resistance and elasticity in the systemic arteries and arterioles, acute changes in ABP do, however, reflect changes in the left ventricular stroke volume (**SV**) and thus in the blood flow. Variations in vascular resistance and elasticity alters the association between ABP and SV; assumptions about changes in cardiac function based solely on changes in ABP then become unreliable (see ABP below).

Many diseases and conditions can compromise *local* blood flow, and may thus threaten the local O_2 supply to, or within, individual organs. An adequate global DO_2 does not guarantee aerobic metabolism in all tissues; it is, however, a prerequisite for this to be possible.

Within each organ system, the balance between local O_2 supply and the tissue metabolic requirements determines whether aerobic metabolism is possible for all cells. In the absence of localized stenosis and occlusions, the O_2 delivery to *individual organs and tissues* is determined by

- The **perfusion pressure** of the blood; in most organs, the pressure difference between the arterioles and veins is representative for the perfusion pressure.
- The l**ocal vascular resistance**, i.e. the balance between vasoconstricting and –dilating mechanisms and the effect of partial occlusion (stenosis, thrombosis, emboli).
- The **pressure exerted by the surrounding tissue** (see below and Part 2-4).

Cardiology is a vast field. The target group for this compendium is medical personnel involved in emergency- and critical care medicine and anesthesia; the focus is therefore on selected aspects

of basic physiology and pathophysiology important for rational treatment in connection with acute disease and trauma. Basic knowledge of the anatomy and conduction system of the heart and circulatory system is assumed known to the readers, and is not described here. A simple, non-anatomical sketch of the central circulation and the relationship between the two ventricles is presented in fig. 3-1.

The heart and the central circulation.

The total flow of oxygenated blood (i.e. the C.O.) necessary to maintain aerobic metabolism in the tissues varies with the metabolic activity of the organism as a whole. In hypothermia, with a body temperature of 24-25°C, the O_2 consumption ($\dot{V}O_2$) is about 50% of normothermic resting

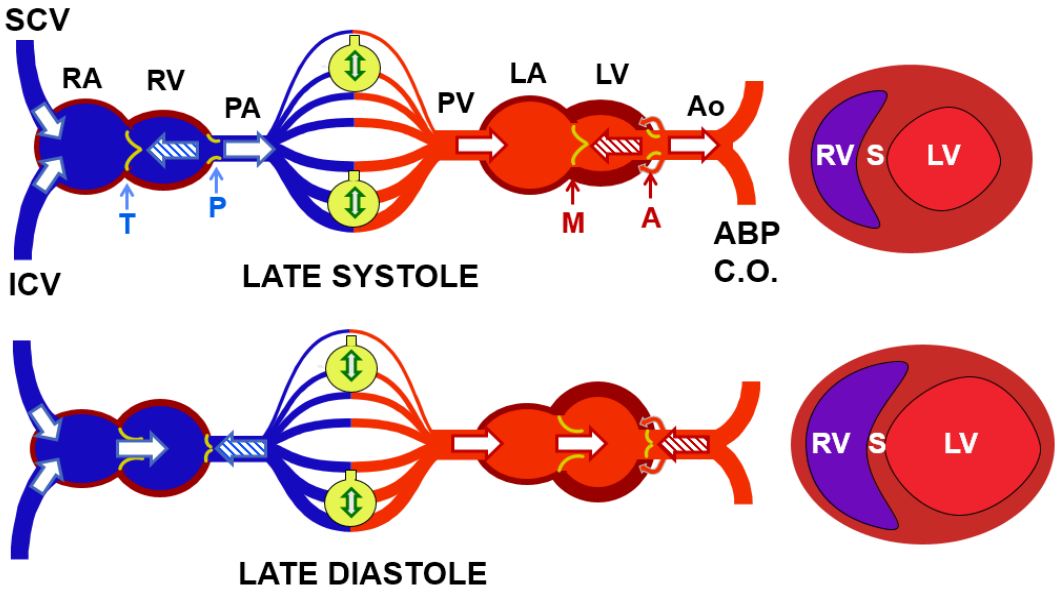

Figure 3-1. *Graphical overview of the central circulation in late systole and diastole. Unfilled arrows show direction of flow, hatched arrows indicate pressures that keep the valves closed. The two major veins (superior and inferior caval veins –* **SCV** *and* **ICV**) *supplies the right atrium* (**RA**) *with blood, which flows on through the tricuspid valve* (**T**) *into the right ventricle* (**RV**) *during diastole. Contraction of the RV ejects part of its blood volume (RV stroke volume,* **RVSV)** *through the pulmonary valve* (**P**) *into the pulmonary artery* (**PA**); *the tricuspid valve blocks regurgitation to the atrium during contraction, the pulmonary valve blocks regurgitation from the PA to the RV during diastole. After perfusing the lung tissue, the blood is collected into the pulmonary veins* (**PV**) *and flows into the left atrium* (**LA**) *before entering the left ventricle* (**LV**) *through the mitral valve* (**M**) *during diastole. Contraction of the LV ejects part of its blood volume (the LV stroke volume,* **LVSV**) *through the aortic valve* (**A**) *into the aorta* (**Ao**), *where the volume of ejected blood is crucial for the arterial blood pressure* (**ABP**). *Together with the heart rate, the LVSV determines the cardiac output* (**C.O.**). *The mitral valve blocks regurgitation to the atrium during contraction, the aortic valve blocks regurgitation from the Ao to the LV during diastole. Also shown is a transverse section of the two ventricles with their common septum* (**S**).
As all structures depicted above lies within the thoracic cavity, changes in airway pressures affect both pulmonary vascular resistance and intrathoracic pressures, and changes the transmural filling pressures on both sides of the heart. The external pressures (except for in pericardial tamponade) have modest effect on the LV per se, but change its end-diastolic filling volumes indirectly (see below).

values; during severe muscular exertion, it may increase to 10 to 20 times the resting value (see Part 2-3).

To fulfill their tasks under varying degrees of O_2 consumption ($\dot{V}O_2$), both ventricles depend on an adequate *inflow of blood during diastole* (i.e. securing an adequate diastolic filling volume – preload). In addition, the *contractile strength of the myocardium* must be sufficient to overcome the resistance to ejection (afterload) of an adequate SV into the pulmonary artery (PA) and aorta (A), respectively. The blood flow from the major veins, through the four chambers of the heart and the lungs, as well as a transverse section of the ventricles, is depicted schematically in fig 3-1 above.

The structures constituting the central circulation (except for the LV and aorta) are thin-walled. Changes in the surrounding *intrathoracic pressure* , therefore, change the venous- and cardiac transmural pressures (Apx), and thus the diastolic blood volume filling the ventricles (the *preload*, see below). Changes in *airway pressure* also affect the vascular resistance in the pulmonary circulation (Part 4-1), and thus also the function of the RV. Changes in RV function may have consequences also for the LV, and thus affect the C.O. (see ventricular interdependence).

The right and left ventricles share a common wall, the cardiac septum. If changes in diastolic pressures on one or both sides may displace the septum, changes in the function of one of the ventricles may therefore induce changes in the function of the other. Such effects are illustrated by schematic drawings of the transversal axis of the ventricles (fig. 3-1) when appropriate.

3-1. NORMAL FUNCTION OF THE HEART: PHYSIOLOGY AND BASIC PRINCIPLES

CARDIAC FILLING AND STROKE VOLUME EJECTION

The cardiac cycle, ejection fraction, stroke volume, and cardiac output (C.O.)

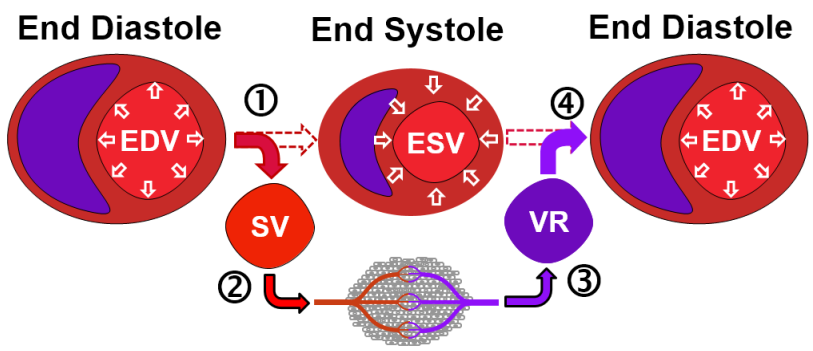

Figure 3-2.
① *During systole, contraction of the left ventricle ejects 50-70% of its end diastolic volume* **(EDV = LVEDV)** *into the aorta, from which it is distributed to the various tissues.*
② *The ejected volume represents the stroke volume* **(SV)**, *i.e. the difference between the EDV and the end systolic volume* **(ESV = LVESV)**. *Its magnitude is determined by the*

- **The LVEDV.**
- **The contractile state** *of the myocardium*
- **The resistance** *against ejection* (**afterload**).

③ *After passage through the tissues, a volume of blood equal to the SV, the venous return* **(VR)**, *fill first the right and then the left ventricle during diastole.*
④ *The magnitude of the LVEDV (representing the* **preload**) *is determined by*

- **The transmural filling pressure,**
- **The compliance of the ventricular walls** *(see text for details).*
- **The time available for filling** *(i.e. the duration of diastole)*

The cardiac cycle consists of two main phases: The **diastole**, in which the relaxed ventricles fill with blood from the atria, and the **systole**, during which the myocardium of right and left ventricles contract and eject a blood volume (a **fraction** of their end-diastolic filling volume) equal to that received from the atria (Fig 3-2). The ejected volume represents the **Stroke Volume (SV)**), which cannot (except for very short periods) be different for the two ventricles. The **SV**, together with the **resistance** and **compliance** of the systemic arterial vasculature, determine the **Pulse Pressure (PP)**, see fig 3-4 below.

In normal sinus rhythm, an electrical impulse is automatically generated by a small group of cells in the right atrium, the **sinus** *or* **sinoatrial (SA) node.** As the impulse spreads out through the myocardial muscle fibers of the atrium towards the ventricles, the fibers contract and increase the pressure in the atrium. When the impulse reaches the **atrioventricular (AV) node** located at the bottom of the right atrium, it follows a bundle of cells with a high conduction speed (the **bundle of His**) towards the apex of the heart. The impulse then spread out through the **Purkinje fibers** to cause a synchronized contraction of the ventricles, starting at the apex and progressing toward the pulmonic and aorta valves.

When the electrical impulses follow this pattern in a normal way**,** i.e. a **normal sinus rhythm**, the result is a synchronized contraction of the atrial, and subsequently the ventricular walls. This impulse pattern coordinates the atrial and ventricular contraction and squeezes the blood toward the orifices; any disturbance of this synchronization (e.g. bundle blocks, arrhythmias) reduces the efficiency of the heart as a pump.

The blood volume within the left ventricle of an average healthy young male at the start of systole, the **Left Ventricular End-Diastolic Volume (LVEDV)**, is about 120-150 ml. The volume remaining at the end of the systole, the **Left Ventricular End-Systolic Volume (LVESV)** is about 40-50 ml. The **SV** is thus about 70-100 ml, and the normal **ratio** between **SV** and **EDV** is about 45-60% for the right ventricle and 50-70% for the left ventricle; the ejected volumes are similar but the end-diastolic volumes of the two ventricles are different (1). The **Ejection Fraction (EF)** is the **ratio** between SV and EDV in the LV, this parameter is a central concept in cardiology for describing the functional state of the heart.

There is a considerable **inter-individual variation** in the above parameters; in addition to changes induced by diseases, age, individual fitness level, sex, body characteristics, genetic variations and therapeutic interventions are well-known factors (2, 3). The total flow of blood to the organism per minute, the **C.O.**, is the product of the **SV** ejected by the left ventricle into the aorta with each heartbeat, and the **heart rate (HR)**:

C.O. = SV x HR.

In diseased hearts, most commonly those with mitral or tricuspid valve insufficiency, but also in persons with septum defects and other anatomical abnormalities, the total blood volume ejected from the left ventricle during systole, and the stroke volume ejected into the aorta, may diverge substantially (Part 3-2).

The normal cardiac response to a decrease in the O_2 content of the blood *or* an augmented O_2 consumption, *or* both, is to increase the C.O. Increases in HR and SV both play a role in cardiac compensation, with the HR contributing the largest percentage of the increase. While a typical mean increase in SV during heavy exertion is around 30%, the HR may increases to about 200% or more above baseline. If the HR increases above 130-150 beats/min in non-athletes, the diastole becomes so short that the end-diastolic filling volume (and thus the stroke volume) does not increase further; increased C.O. beyond this point is purely a function of increased heart rate (4). In endurance-trained athletes, however, diastolic filling and stroke volume may increase until maximal heart rate is achieved (5). The capacity of the heart to augment the C.O. decreases with increasing age; the reduction is more due to a reduction in the maximal HR than in the SV (6).

The left ventricular pressure-volume loop

Both systole and diastole may be divided further into two subsets of phases (see below); the relationship between intraventricular pressures and volumes during the four phases constitute the **pressure-volume loop** for the ventricles (see Fig. 3-3 and below for details). The area enclosed by such loops is representative of the **amount of mechanical work** performed by the myocardium, which also reflects the amount of O_2 consumed by the heart during a cardiac cycle (7, 8).

The four phases constituting the pressure-volume loop for the left ventricle are depicted in figs 3-3 and 3-4. The numbers in the text below refer to the numbers in fig. 3-3. The percentages quoted below and shown in fig. 3-3 and 3-4 are mean values for healthy hearts beating at a rate of 70-75 beats pr. minute (9).

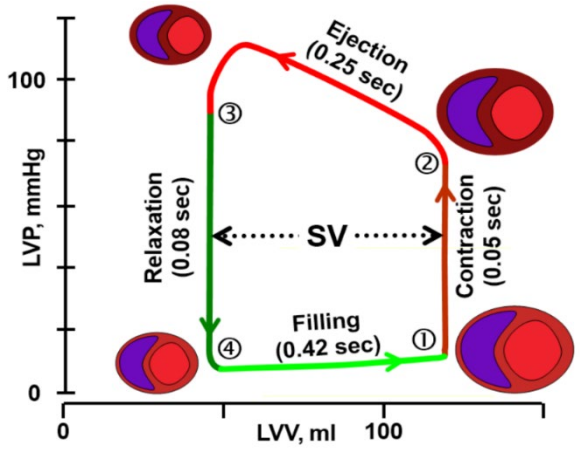

Figure 3-3. *Graph depicting the four phases of the cardiac cycle and the pressure-volume loop of the left ventricle. See text for details.* **SV:** *Stroke volume.* **LVV***: LV volume,* **LVP***: LV pressure.*

Systole: Isovolumetric contraction (starting at ① in fig 3-3 and fig 3-4) is the initial part of the systole and represents about 6-7% of the time for a total cycle. When the ventricles start to contract (corresponding to the *start of the QRS complex* in EKG), the intraventricular pressure rises; when the ventricular pressures *exceed* the atrial pressures, the mitral and tricuspid valves close. After this, the blood volume of the ventricles remains constant until the ventricular pressures become *higher* than the diastolic pressure in the recipient vessels (aorta or pulmonary artery, respectively). In the systemic arteries, this corresponds to the blood pressure at the end of diastole (fig. 3-4).

Systole: The ejection phase (starting at ②) is the second phase of systole and represents about 23-31% of the total cycle. Ejection starts when the intraventricular pressures become higher than that in the recipient vessels, the blood starts to flow out of the ventricles; the flow continues for as long as the intraventricular pressures remain higher than those in the aorta or the pulmonary artery. When this is no longer the case (i.e. when myocardial contraction ceases and diastole commences), the aortic- and pulmonary valves close. In the systemic arteries, the magnitude of the stroke volume ejected into the aorta is a major factor in determining the systolic arterial blood pressure (**SABP**) (fig. 3-4). **Diastole: Isovolumetric relaxation** (starting at ③) commences when ventricular contraction ceases and the heart muscle relaxes (preceded by the T *wave* in the EKG), and represents 10-12% of the total cardiac cycle. When the intraventricular pressures fall *below* that of the aorta/pulmonary artery, their respective valves close, after which the intraventricular pressure falls rapidly. During this phase, the volume of the ventricles (the end-systolic volume) remains constant until the intraventricular pressures fall below those in the atria, after which the mitral and tricuspid valves open and diastolic filling starts. *In the arteries* , this phase corresponds to the initial post-systolic decrease in pressure (dicrotic notch, see fig. 3-4).

Diastole: Filling of the ventricles (starting at ④) occurs as the ventricles of the heart are progressively dilated by the pressure created by the blood returning to the atria through the large veins while the aortic and pulmonary valves are still closed. The filling phase represents about 53-58% of the total cycle; there is a rapid early filling phase (due to initial increased atrial pressure relative to the ventricular), followed by a slower phase as the pressure difference decrease. *In the arteries* , this phase is characterized by steadily decreasing diastolic pressures as the stroke volume is distributed to the various organs (fig. 3-4). Towards the end of the filling phase, a contraction of the atria (the *P wave* in the EKG) produces a brief increase in filling pressure which further increases the end-diastolic volume of the ventricles and may add as much as 20% - 30% to the end-diastolic filling volume (10). Loss of the atrial contraction has, in animal experiments, been found to reduce the stroke volume by 20% - 37%, depending on heart rate (11).

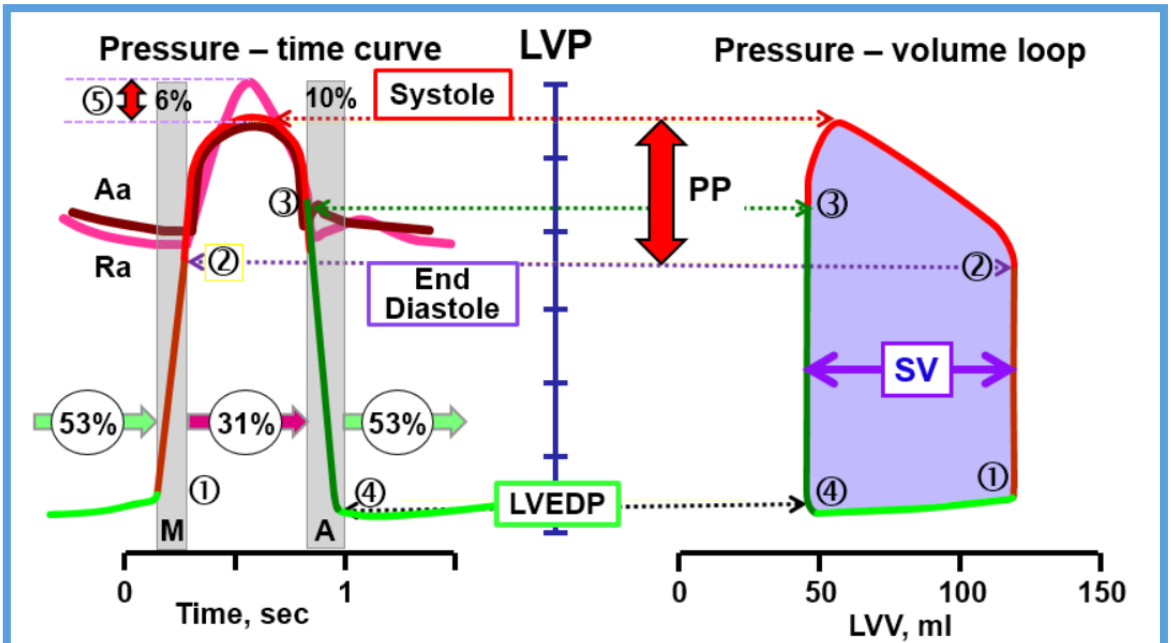

Figure 3-4. Pressure-time *and corresponding* **Pressure-volume** *curves for the left ventricle. Grey columns in the pressure-time curve indicate the iso-volumetric phases; in column* **M,** *the mitral valve closes* ① *and aortic valve opens* ②*. In column* **A**, *aortic valve closes* ③ *and mitral valve opens* ④*. Pressure curves, as measured in the ascending aorta (***Aa***) and the radial artery (***Ra***), relative to the phases in the cardiac cycle, are also shown. The* **pulse pressure (PP)** *is the pressure interval between peak systole and end diastole* ②*. The difference in systolic pressure between* ***Aa*** *and* ***Ra*** *is shown by the red arrow* ⑤*, upper left (see also Arterial Blood Pressure).*

The final end-diastolic left ventricular filling volume (LVEDV).

In normal hearts, the LV volume at the end of diastole - the **LVEDV** - is **representative of its preload** (see below for definition), which is an important determinant for both the strength and speed of systolic myocardial contraction (see Frank-Starling mechanism below). The **LVEDV** is mainly determined by three factors (see also fig. 3-2):

- The **Left Ventricular End-Diastolic Pressure (LVEDP)**, i.e. the net filling pressure of the blood in the left ventricle at the start of systole and the time available for the filling phase.
- The **intrinsic compliance of the myocardium (C)** varies from person to person, compliance changes occurs as a result of ischemia, fibrosis, hypertrophy, myopathies, etc.
- **External pressures on the heart** (e.g. pressures exerted on the heart and large intrathoracic vessels by pericardial fluid, pneumothorax, and/or positive pressure ventilation) may change the diastolic filling of both ventricles by reducing the *effective* or *transmural* diastolic pressure (see Apx). Changes in transmural pressure may be reversible within seconds if the external pressure is relieved (e.g. drainage of air in pneumothorax, of blood in hemothorax, or of fluid in the pericardium), suddenly increasing or normalizing the LVEDV.

In addition, variations in **heart rate** change the time available for diastolic filling; severe tachycardia limits the time available and may reduce the LVEDV (see below).

The left ventricular end-diastolic filling pressure, **LVEDP**, has sometimes been used as a semi-quantitative indicator of the preload. Due to substantial individual variations in myocardial compliance, the correlation between filling *pressure* and -*volume* is often poor. In addition to the

effect of diseases *per se*, therapeutic interventions (e.g. increased airway and intrathoracic pressures) may affect the effective ventricular compliance (see below). Using ventricular filling pressures *alone* as a surrogate for their filling volume (i.e. the preload) can lead to serious errors in both diagnosis and choice of therapeutic interventions (see also Part 3-4, PA catheter).

The cardiac cycle and perfusion of the myocardium.

The perfusion of the cardiomyocytes in the left ventricle, particularly in the part that is closest to the endocardium, occurs mostly during diastole; the right ventricle, where the wall tension during systole is much lower, is perfused during the whole cycle (1). As a consequence, the mean diastolic arterial pressure (i.e. the mean pressure *after* the closure of the aortic valve) is most relevant for the perfusion pressure of the left ventricle, while the mean arterial pressure, MAP, is more relevant for the perfusion of the right ventricle. If the right ventricle hypertrophies due to chronic high pulmonary artery pressures, however, the perfusion conditions of the right ventricle become more like the left (1).

In general, increased heart rate leads to a more pronounced reduction in time for diastole than for systole (1); tachycardia, therefore, increases the risk of ischemia in the myocardium, especially in persons with coronary artery stenosis.

Relationship between stroke volume and ejection fraction (EF).

As the ejection fraction (EF) is defined by the ratio between stroke volume (SV) and LV end-diastolic volume (LVEDV), a given SV results in different EFs when the LVEDV varies. Two patients with an identical SV and C.O., but different LVEDV, may thus have substantially different EFs; different SVs may yield identical EFs if there is a corresponding change in end-diastolic volume (see fig. 3-5). The EF, while an important parameter in both diagnosis and prognosis in cardiac disease, is therefore *not synonymous with the output capacity of the heart* at the time of measurement. In general, however, a low EF, especially if combined with a dilated ventricle, signals a reduced cardiac reserve capacity.

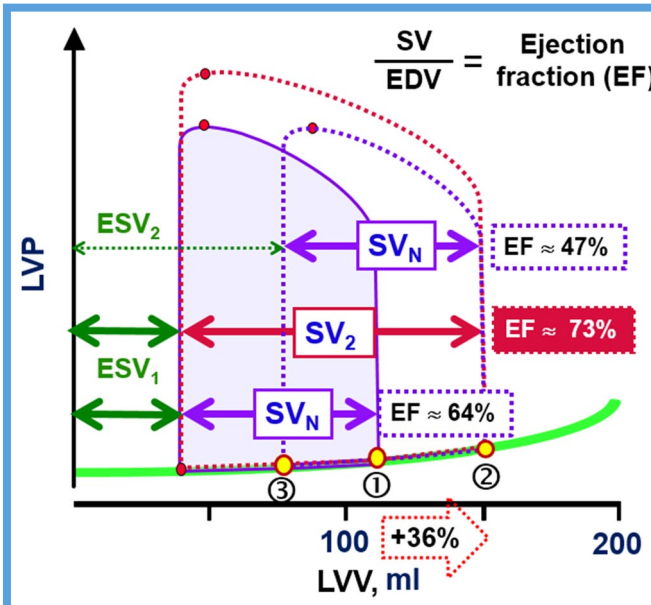

Figure 3-5. The ejection fraction (**EF**) *of the left ventricle is the ratio between the stroke volume* (**SV**) *and the end-diastolic volume. If the normal SV* (**SV_N**) *is 70 ml and EDV 110 ml, the EF is 0.64 or 64% (blue area). Increasing the SV* (**SV_2**) *by 36% when increasing the EDV (from ① to ②, red dots) and maintaining the end-systolic volume (ESV_1), gives an EF of 0.73 or 73%. If the ESV increases (ESV_3) to ③, and the original SV of 70 ml is main- tained* (**SV_N**) *at the higher ESV (violet dots), the EF becomes 0.47 or 47%.*

In the systemic circulation, the *SV* of the left ventricle and the *elasticity and resistance in the vasculature* (together with the end-diastolic arterial pressure, which is reduced in bradycardia because of the increased time available for distribution of the SV to the tissues) determine the systolic blood pressure (see Blood pressure below).

The stroke volumes and their frequency are important for the DO_2, the **stroke**

work (SW) is often used as a measure of the *contractile* force of the left ventricle (see below). It is defined as the SV multiplied by the systemic perfusion pressure, i.e. the difference between mean arterial pressure and left atrial pressure (LAP):
SW = SV x (MAP-LAP),
or approximately the *area within the pressure-volume loop* (fig. 3-3 above).

DETERMINANTS OF THE STROKE VOLUME: PRELOAD, AFTERLOAD, AND MYOCARDIAL CONTRACTILITY

Most of our basic knowledge about the effects of acute changes in cardiac preload and afterload on the pumping capacity of the heart is based on experiments in healthy animals or utilizing organs and tissue from such animals. Much of this knowledge have later been corroborated by investigations of cardiac function in healthy humans; there are, however, substantial variations in the relationship between ventricular filling pressures and -volumes within groups of normal individuals assumed to be healthy (see below). In persons with cardiac disease, and/or other conditions that affect cardiac function, the ability to increase the C.O. in response to reduced O_2 content of the blood may then be attenuated or lost.

The Frank-Starling law of the heart.

The German physiologist Otto Frank, investigating the strength of myocardial contraction in isolated frog hearts (12), found that increasing the ventricular filling volume also increased the strength of contraction. Similar results were later found by the English physiologist Ernest Starling and co-workers, who used a canine heart-lung preparation and measured changes in the C.O. as a consequence of increasing the atrial pressure, and thus the filling of the ventricles (13, 14). Starling formulated his "law of the heart" stating that "The larger the diastolic volume of a given heart, the greater is the force of contraction which immediately ensues" (15). The shape of the Frank-Starling curve (fig. 3-6) is based on the observations of these scientists, although none of them presented the curve bearing their names in the shape usually shown today. While the Frank-Starling mechanism is important for the ability of the heart to cope with acute (seconds-minutes) increases in demands on the circulation, longer and frequent periods of ventricle dilatation may lead to myocardial hypertrophy, with long-term negative effects on cardiac function.

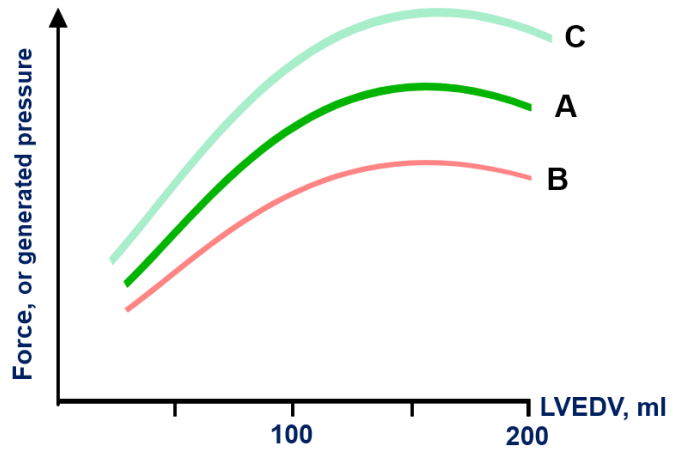

Figure 3-6. *The* **Frank-Starling** *curve, describing the relationship between left ventricular end diastolic volume and force of contraction of a normal heart. The ascending part of the curve is close to linear for end diastolic volumes within the normal range.* **A***: Normal curve.* **B***: Reduced myocardial contractility.* **C***: Increased contractility.*

Deviations from the "normal" Frank-Starling curve.

The shape and position of the Frank-Starling curve is altered when the work conditions of the heart change (e.g. variations in myocardial diastolic compliance and contractility, myocardial O_2 supply, resistance to ejection of the stroke volume); i.e. the same heart may display different curves under different conditions (16), see fig. 3-6.

Even if Starling, and later the American physiologist Sarnoff and co-workers (16), stated that the important factor for determining the force of myocardial contraction was the end-diastolic *volume* (or *preload*, see below), they both employed filling *pressures as a surrogate for volume* when presenting their results.

This led, unfortunately, to considerable confusion; as filling pressures during many decades were much easier to measure than filling volumes; the Frank-Starling mechanism was sometimes presented using filling pressures instead of volumes on the X-axis, thus corrupting the preload principle. Displaying the relationship between filling volumes and force of contraction utilizing pressure-volume loops for the left ventricle (see figs 3-3 and 3-4, also reviewed in ref. 17) facilitates understanding of the true relationship between preload and afterload.

Definitions of preload and afterload, using isolated myocardial muscle.

The concepts of *preload* and *afterload* were originally introduced during the middle of the 1800-ties in experimental investigations measuring the strength of skeletal muscle contraction. It was re-introduced in the 1930-ties (18) as a method to describe the condition of stretch in experiments involving strips of myocardial muscle, often isolated cardiac papillary muscle (19, 20, 21). In such experiments, the muscle strips are suspended from one arm of a lever system with the lower end fixed to a tension transducer (fig. 3-7). By placing small counterweights of varying mass on the opposite arm of the scale before contraction was induced, the muscle fibers can be stretched to various lengths. Within the physiological range of stretch, increased preload, as determined by the mass of the counterweight, augments the **degree of stretch** of the muscle fibers**.**

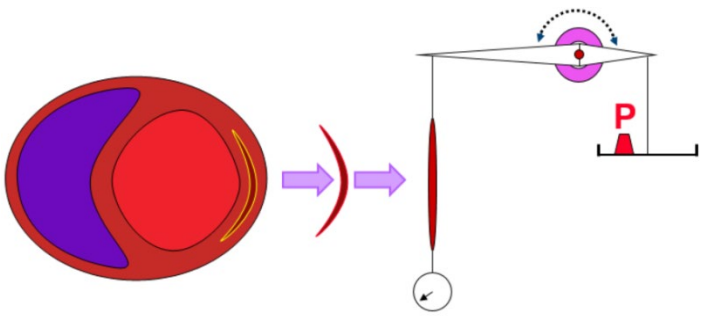

Figure 3-7. *Preload measurement. An isolated strip of cardiac muscle is fixed to one arm of a scale. By placing counterweights (***P** *– preload) on the opposite arm, the fibre can be stretched to the desired length. The degree of stretch is similar to the stretching of the myocardial fibres during diastolic filling, the filling volume is therefore representative for the preload***.**

After achieving the desired degree of muscle stretch, a stopper above the arm suspending the muscle strip was adjusted to avoid further stretching when an additional counterweight was added (fig. 3-7). When a muscle contraction was induced by an electrical stimulus, the **total weight that could be lifted** by the muscle contraction, **the afterload,** defined the power of muscle contraction. In this type of experiment, increased stretch of the muscle fiber (*increased preload*) within the physiological range enabled the muscle strips to either lift a heavier mass (isotonic contraction) or generate a higher tension during constant length (isometric contraction). This relationship is in agreement with the Frank-Starling curve found by experiments on isolated hearts (fig. 3-6).

After reaching a certain degree of stretch, a further increase in the preload did not increase the capacity for lifting a heavier afterload (i.e. increase the power of contraction), corresponding to the *flat* part of the Frank-Starling curve. At this level of stretch, the non-elastic constituents of

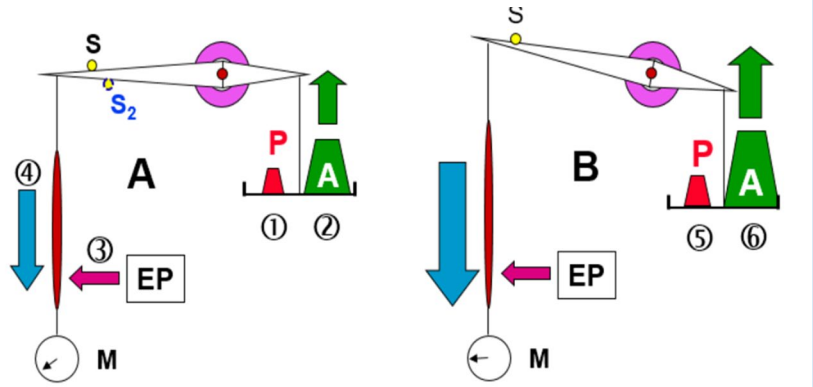

Figure 3-8. Panel A. *After achieving the desired preload (see fig 3-7 above), a stopper* (**S**) *inhibits further stretch of the fibre when an additional weight* (**A**) *is added. When stimulated by an electrical impulse* (**EP** ③)*, the fibre contracts* ④*; the mass of the weight lifted* (② + ①) *defines the force of contraction, the* **Afterload***. If a second stopper* (**S_2**) *and a sensor* (**M**) *is added, the force of isomeric contractions can be measured.*
Panel B. *By increasing the stretch of the muscle fibre (preload), its force of contraction can lift a heavier mass* (⑥ +⑤)*; i.e. it can overcome a larger afterload.*

myocardial tissue (collagen and other fibers) probably inhibit further stretching of the cardiomyocytes (22).

The addition of *catecholamines* (e.g. adrenaline) to the fluid perfusing the muscle fibers or an isolated heart enhances the muscular *contractility* (strength of the contraction, i.e. enabling the lifting of a heavier afterload at a given preload). An *increased heart rate* also increases the contractility of the heart by changing the intracellular flow of Ca^{++} (the "Bowditch effect", see ref. 23). Other agents that increase the cellular content of cyclic adenine monophosphate (cAMP) *or* change the intracellular metabolism of Ca^{++} also increase the contractility of the heart (Part 3-4, Therapy).

Preload and afterload in the intact heart.

Translated into conditions of the intact heart, the **end-diastolic volume** of the ventricles (*not* the pressure within the chambers, *nor* the transmural pressure) determines the stretch of the muscle fibers before the contraction starts. In persons with a normal configuration of the ventricle, this volume is often defined as the **ventricular preload**. An increase in end-diastolic volume augments the contractile force of the ventricle (see below). The **sum of all factors** that must be overcome during ejection of the stroke volume (see impedance below) represents the **afterload**.

If the heart is *over-filled* , pumping capacity may decline once more. The walls in the chambers of the heart become thinner the more the heart is dilated, and this reduces its speed of contraction (Laplace's law). Over-stretching of the mitral valve apparatus in a dilated heart may cause functional mitral valve insufficiency, further reducing the pumping capacity of the heart (16, 24).

The ventricular filling volume may be calculated relatively exactly in the laboratory with the aid of computerized x-ray (CT), cardiac magnetic resonance (MR), or nuclear isotopic examinations. It may also be estimated by echo cardiography (ECHO). Although the latter method is slightly less exact, it can be performed repeatedly at the bedside, in emergency and intensive care wards, and in operating theatres. Bedside, assumptions about a qualitative relationship between end-diastolic filling pressures (low, medium, high) and corresponding volumes (hypovolemia, normal, hypervolemia) is reasonable in patients without known or suspected heart disease, and if corrected for the effects of increased intrathoracic pressures and other known confounding factors. A measurement of filling pressure *alone* cannot be translated into assumptions about the filling volume (25), see below.

The normal diastolic pressure-volume curve.

The ability of myocardial muscle fibers to stretch when exposed to a given transmural pressure during diastole (also called lusitropy) can be illustrated by the pressure-volume curve for diastolic filling of the heart (10, 17). In healthy hearts, a relatively standardized curve describes the relationship between the left ventricular end-diastolic volumes (LVEDV) and the corresponding filling pressures (LVEDP) (fig. 3-9). The curves for the right and left ventricles are not quite similar. The filling pressures (roughly represented by the **CVP** in the case of the right ventricle, and by the pulmonary wedge pressure, **PCWP**, or "occlusion pressure", **PAOP**, in the case of the left ventricle) are different (26) as are the end-diastolic volumes (1). The effect of the short pressure increase towards the end of diastole, the "atrial kick" (10) on the filling volumes, is not well depicted by such curves when mean values for the filling pressures are employed. Rough calculations of filling pressures can also be made by estimates of vascular diameters and flow during echo-doppler cardiography (ECHO), but these are less reliable than pressures measured during heart catheterization (27).

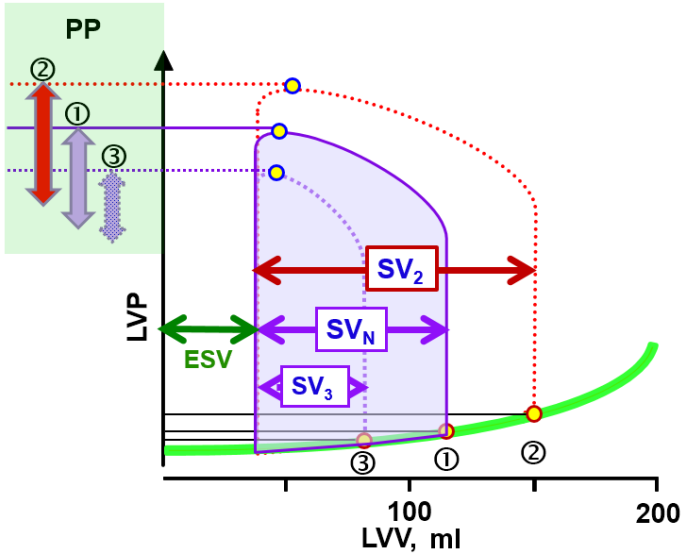

Figure 3-9. *The left ventricular end-diastolic curve (green) depicting end-diastolic filling volumes (LVEDV) as a function of filling pressures in a heart with normal SV* (**SV_N**)*. Increasing the LVEDV (from ① to ②, red dotted curve) increases the contractility, the SV* (**SV_2**) *and pulse pressure (PP, upper left) if the end-systolic volume (ESV) remains constant. Decreased LVEDV (from ① to ③, lilac dotted curve) reduces the SV* (**SV_3**) *and the PP.*

In spontaneously breathing persons with normal hearts, the relationship between end-diastolic filling pressures and -volumes at low filling volumes consists of an almost straight line with a low rate of rising pressure. With an increasing stretch of the cardiac fibers, the line changes into an exponential curve (28) (see fig. 3-9). In healthy persons at rest, filling pressures on the right side are lower than on the left side (mean difference 4 mmHg, range 1-7 mmHg, ref. 10). In disease, however, the relationship between the right and left filling pressures may be changed; either as a more pronounced difference (left ventricular diastolic dysfunction with preserved right ventricular function – as in acute myocardial infarction involving only the left ventricle) or reversed (as in pulmonary vascular hypertension), Part 3-2.

Deviations from the normal pressure-volume curve.

Disease and therapeutic interventions may change the position as well as the shape of the end-diastolic pressure-volume curve (fig. 3-10), mainly by displacing it upwards (29). The end-diastolic filling volume corresponding to a given pressure is then decreased even if the compliance of the myocardium *per se* is normal (fig. 3-11). Disease states affecting the cardiac muscle itself, such as *cardiac hypertrophy*, *fibrosis*, and acute and chronic *myocardial ischemia* may decrease the heart's compliance and make the configuration of the pressure-volume curve steeper (30)(fig. 3-10). Changes in the diastolic transmural pressure of the heart (e.g. *cardiac tamponade*, *positive pressure pneumothorax, hemothorax*) also change the configuration of the

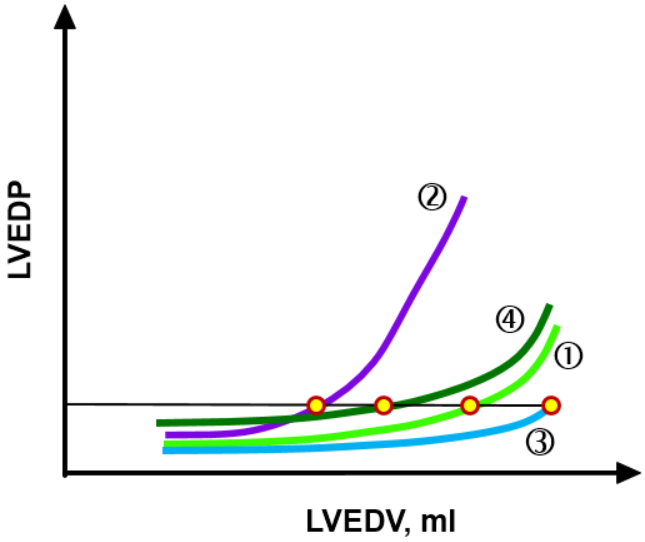

Figure 3-10. *Three types of changes from normal position and shape ① of the end-diastolic pressure-volume curve. Curve shifts due ② reduced myocardial compliance, ③ increased compliance and ④ increased intrathoracic pressure are shown for comparison. Note that the same filling pressure (as measured relative to the ambient pressure) may correspond to widely different diastolic filling volumes (red-and–yellow circles).*

pressure-volume curve of normal hearts in the same way. On the other hand, sepsis may *increase* cardiac compliance (31), making the curve less steep (see below and fig. 3-10).

Therapeutic interventions that increase intrathoracic pressure (e.g. continuous positive airway pressure (CPAP) and positive pressure ventilation (IPPV), Part 4-4) also change the configuration of the curve (fig. 3-11) and the end-diastolic pressure-volume relationship.

Unfortunately, the relationship between filling pressure and –volume also exhibits substantial variations in persons assumed to be in good health (32). Positive pressure ventilation, which is common during general anesthesia and in intensive care, shifts the curve upwards even if the heart *per se* is healthy (fig 3-11). This makes inferences about the blood volume status, based on filling pressures alone, hazardous (33). An isolated measurement of filling pressure (i.e. CVP, PCWP) does *not* represent reliable information about the left ventricular preload, or whether interventions to change it are needed (25, 34, 35, 36).

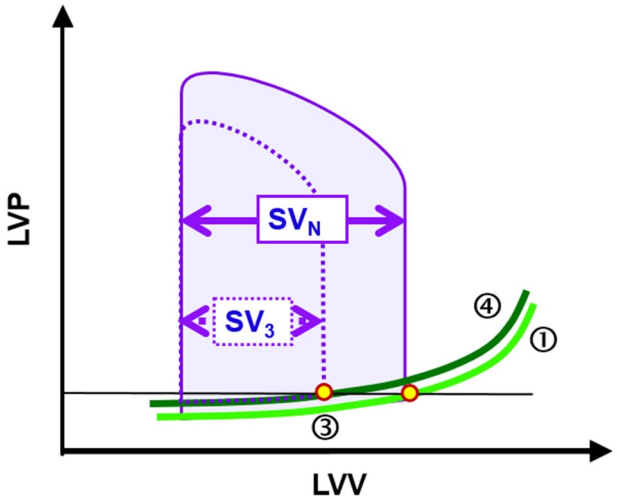

Figure 3-11. *Effect of increased intrathoracic pressure (e.g. continuous positive pressure ventilation, CPPV) on left ventricular end-diastolic pressure-volume curve ④ and* **SV** (**SV_3**)**,** *compared to normal curve position ① at the same filling pressure* (**SV_N**) *(see also fig 3-10 above).*

Failure to take these limitations into account may lead to incorrect assumptions about the blood volume and end-diastolic volumes. It may be one of the reasons why interventions based on filling pressures of either the right (37, 38) or the left (39, 40, 41, 42) ventricle as a surrogate for LV preload generally have failed to reduce morbidity and mortality. Another possible explanation for the lack of effect of such measurements on patient outcome may be that in severely ill ICU patients, pro-inflammatory and other signal cascades have already established a change in the function of many organs. If the metabolic functions of the cells are already compromised, efforts to optimize circulation after this stage has been reached cannot be expected to affect the

outcome of such patients.

The caveats above do *not* imply that measurements of filling pressures are worthless in all situations. In the western world, most severely ill patients have a central venous catheter (CVC) inserted, offering ready access to measurement of pressures in a major intrathoracic vein (and also to obtain samples for blood gas analysis, Part 5-4). In patients with a clinical picture of circulatory failure combined with a *low* central venous pressure (CVP), it is safe to assume that *hypovolemia* or *pathological vasodilation* represents at least part of the problem. A trial infusion of fluids is then warranted. The interpretation of CVPs in the upper normal or high range is more complicated (see below). Very high levels (i.e. > 20-25 mm), however, should incite suspicion about *either* a possible RV failure *or* pathological increases of the intrathoracic/intrapericardial pressures as causes of the problem.

Force of contraction and ventricular stroke volume.

When ejecting the stroke volume into the aorta**,** the force of cardiac muscle contraction must overcome the forces that resist ejection ("afterload"). The balance of these forces regulates the stroke volume. The contractile strength of the myocardium is mainly determined by

- The **preload** (i.e. the stretch of the myocardial muscle fibers, i.e. the Frank-Starling effect) and
- The **intrinsic contractile force** of the myocardium.

The effect of preload on the force of the myocardium.

With augmented end-diastolic filling volume, the increased contractility created by increased myocardial fiber stretch or preload (see above) enables the heart to pump the same stroke volume against a higher pressure, i.e. higher vascular resistance or afterload. If, on the other hand, the pressure is kept constant (e.g. by physiologic, pathological, or drug-induced vasodilation), the stroke volume increases (fig. 3-12, also 3-13). If the heart contracts against a fixed resistance to ejection, increasing the LVEDV increases the pressure generated during systole.

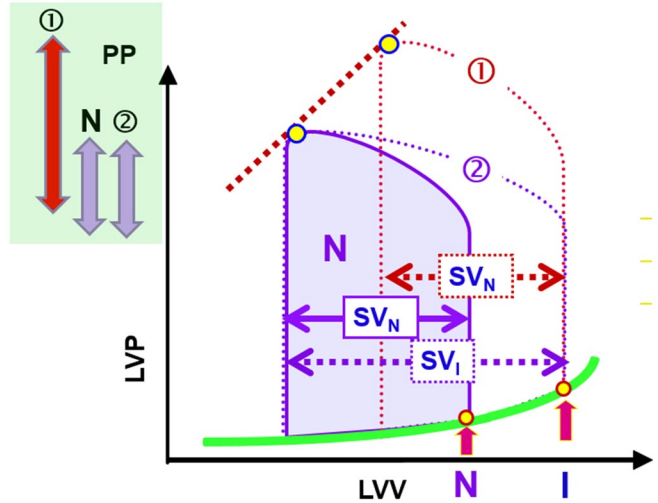

Figure 3-12. *Graph showing the increased force of LV contraction created by increased preload.* **N** *=normal LVEDV and corresponding pressure-volume loop. An increased LVEDV* (**I**) *can be utilized to maintain a normal SV* (**SV_N**) *in the face of increased resistance and thus SABP* ①, *or to increase the stroke volume (loop* ② and **SV_I**) *if the resistance is reduced by vasodilation (SABP stable). The resulting pulse pressures are shown in the upper left, green area.*

This effect can be illustrated using an animal model where the major vessels are tied off, the aortic valve is incapacitated and the LVEDV can be varied using a cannula inserted into the left ventricle (43). For LVEDVs within the normal physiological range, the peak pressures corresponding to increasing LVEDVs create an almost straight line, the **End Systolic Pressure-Volume Relationship**, **ESPVR** (28). This line resembles the (close to linear) ascending part of the Frank-Starling curve (figs 3-6 and 3-13).

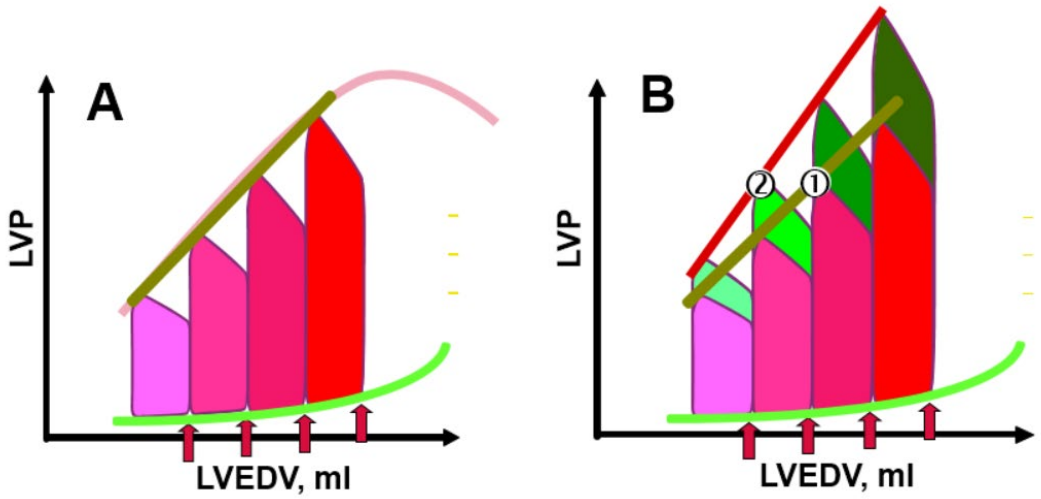

Figure 3-13. A. *Graph showing left ventricular pressure-volume curves under experimental conditions. The increase in maximum force, relative to preload increase, is close to linear (dark green line) within the physiological range of filling volumes. The corresponding part of the Frank-Starling curve (pink curve) is also shown.* **B.** *If the contractile force of the myocardium is increased by addition of adrenaline, the line of maximal contraction shifts upwards and to the left (red line) and becomes steeper. The same force can then be obtained at lower filling volumes and pressures (② compared to ①). A reduced contractility would shift the line of maximal force downwards and to the right of line* **①.**

Intrinsic changes in contractile force.

Regardless of preload, an augmented sympathetic stimulation and/or increased levels of circulating catecholamines increase contractility and heart rate, but also increase the O_2 consumption of the myocardium and increase the risk of arrhythmias (44). Increased levels of thyroid hormones also increase contractility and heart rate; simultaneously, systemic vascular resistance decreases (45). On the other hand, stimulation of the vagal nerve decreases the contractile state (46). Many drugs, toxins, and diseases also induce a negative change of the myocardial contractility.

Left ventricular afterload: effects of arterial vessels and blood viscosity.

To expel the SV into the aorta, the force of myocardial contraction must overcome the counter-forces represented by

- **The peripheral vascular resistance** and/or the resistance created by *subvalvular* (muscular) or *aortic valve stenosis* .
- **The viscosity of the blood,** which usually is proportional to the erythrocyte mass (in most patients proportional to the Hb levels) but may also be affected by an abnormal the mass of proteins (especially globulins) in a non-linear manner, see also Apx.
- **The elastic properties** (elastance) of the vascular beds can be considered as an element of the resistance against the ejection of the SV, as a highly compliant vascular bed has a similar effect on resistance to ejection as a reduction in vascular resistance, and *vice versa* .

The counter-forces that must be overcome by the contracting ventricle during ejection are often lumped together by the expression **impedance**, a composite term (borrowed from physics ter-

minology) that depends not only on viscous resistance but also on the "compressibility, compliance, inertance, and the frequency of imposed oscillations" in the vascular bed (47). Thus, the **force** necessary to overcome the combined effect of these components and eject a given stroke volume from the ventricle represents the **afterload of the ventricle**.

The systolic arterial blood pressure (**SABP**) is often used as a surrogate indicator of the left ventricle afterload (i.e. the afterload increases when the ventricle must eject the stroke volume against a higher pressure or resistance, see Stroke Work above). Such interpretation of the SABP rests on the assumption that ***i)*** the measured arterial pressure does not deviate significantly from that in the aorta *and* ***ii)*** there is no mechanical (e.g. aortic valve stenosis) or dynamic (e.g. subvalvular stenosis) obstruction to the LV outflow.

The stroke volume of the normal heart is determined by a combination of

- **The end-diastolic filling volume** (*preload*) of the ventricles, which is determined by the **transmural filling pressures** *plus* the **compliance of the ventricles** (intrinsic and external factors, see Apx and fig. 3-2) *as well as* the **time** available for filling. Increased preload augments the contractile force of the myocardium.
- **The contractile state** of the myocardium, which may be changed by a multitude of positive and negative factors.
- **The afterload**, or the *total force* that must be generated to overcome the resistance during ejection of the SV (see above). Increased ejection resistance requires an increased myocardial force of contraction to generate the same stroke volume. The **pressures** in the pulmonary artery and the aorta are determined by the stroke volumes and the respective vascular resistances and elastances.

As the normal stroke volume varies with body mass, which is again related to the calculated body surface area (BSA), it is often indexed and called the stroke index, SI (SI=SV/BSA, se Apx). While the stroke volume is an important factor for the output capacity of the heart, increasing the heart rate is even more important for maintaining or increasing the C.O. during acute situations where a mismatch between DO_2 and $\dot{V}O_2$ threatens (48, 49, 50, 51).

Right ventricle (RV) function, ventricular interdependence.

The major tasks of the RV are to ***i)*** drain the O_2-depleted blood from the venous system *and* ***ii)*** supply the volume of re-oxygenated blood to the LV (provided adequate pulmonary gas exchange) necessary for maintaining an adequate diastolic filling of the LV (i.e. preload). To accomplish this, it must have a *low mean diastolic pressure* allowing efficient venous drainage *and* contract with a force that can

- **Overcome the resistance** of the pulmonary vascular bed (normally very low), *and*
- Maintain a pulmonary vascular pressure that **secures perfusion of most of the ventilated alveoli** (Part 4-1).

Although the geometry and volume of the RV differ from the LV, and the resistance to ejection of the SV by the RV is much lower, the effects of variations in preload and afterload are similar. In animal experiments, circulation *can* be well maintained despite the loss of RV contraction if the constraints of the pericardium are removed (52); for many years, such findings downplayed the role of the RV in circulatory failure.

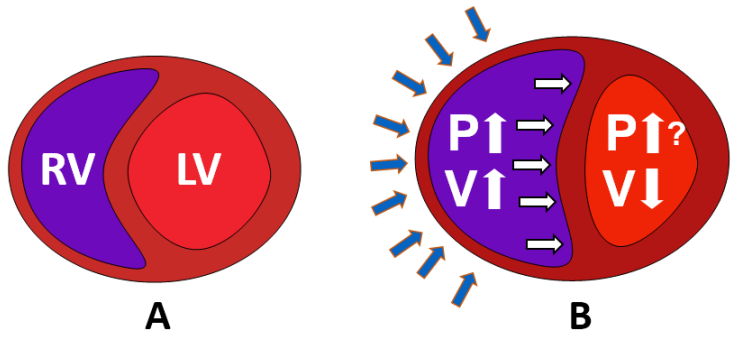

Figure 3-14. Ventricular interdependence.
A: *Cross section of normal right* (**RV**) *and left* (**LV**) *ventricles at end diastole.* **B:** *When diastolic RV pressure* (**P**) *increase relative to the LV pressure, the ventricular septum deviates and reduces the end diastolic volume* (**V**) *of the LV. This effect is compounded by low LV filling pressures (low RV output) and increased pericardial or intrathoracic pressures (blue arrows).*

As the stroke volume of the LV cannot exceed that of the RV for more than a few heartbeats, the RV output is crucial to the LV preload. In humans, failure of the RV is an independent mortality risk factor (53). Ventricular interdependence (54) (i.e. when a dilated RV with a high end-diastolic pressure impedes diastolic filling of an otherwise normal LV when the pericardium is intact), may be a contributing factor to this (fig. 3-14).

Intrathoracic pressure and diastolic filling.

Expansion of the thoracic cage during spontaneous inspiration reduces the intrathoracic pressure, i.e. the pressures surrounding the heart and great vessels become more negative (see fig. 3-15 and 3-16). If the intravascular and intracardiac pressures (relative to atmospheric pressure) are unchanged, the transmural (i.e. the *net distending* pressures) increase. On the other hand, interventions that significantly *increase* airway and/or intrathoracic pressures result in *increased* intrathoracic pressures and *reduced* transmural pressures (fig. 3-15). As the vascular capacity of the pulmonary vascular bed also varies during the ventilatory cycle, the effects of ventilation on the function of the right and left ventricles differ (see below).

An *increase* in intrathoracic pressure may be caused by *spontaneous activities* (e.g. performing a Valsalva maneuver, creating an expiratory resistance by pursing the lips), *or* be a result of

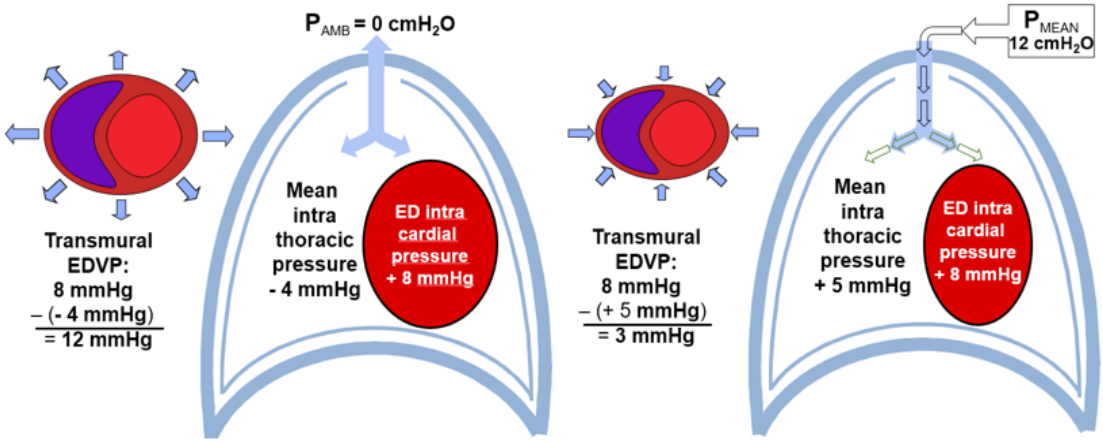

Figure 3-15. *The effect of increased intrathoracic pressures (during CPAP and IPPV) on end-diastolic filling volumes of the heart.* **Left:** *conditions during spontaneous ventilation.* **Right:** *during positive pressure ventilation (IPPV). Re-establishing the transmural end-diastolic* (**ED**) *volumes during IPPV requires increased filling pressures.*

therapeutic interventions (e.g. application of continuous positive airway pressure, CPAP, during spontaneous breathing, or during controlled positive pressure ventilation - IPPV, Part 4-4). The reduction of the transmural diastolic pressure in intrathoracic veins and cardiac chambers during increase in intrathoracic pressures *reduce* the biventricular preload during normo- or hypovolemia and may reduce the C.O. In *over-distended ventricles* with a functional mitral valve insufficiency (55) (Part 3-3), however, reducing the filling volume and thus the annulus circumference may decrease the valve dysfunction and increase the C.O.

Effect of ventilation on the LV stroke volume.

Spontaneous ventilation and preload.

Intrathoracic pressures decrease during spontaneous inspiration (Part 4-1); the decrease is augmented when tidal volumes increase. As the pressure surrounding the large veins and the heart decreases, the *transmural filling pressures on both sides* of normal hearts *increase*. Accordingly, the filling volume of the right ventricle, and thus its SV, rises during inspiration (fig. 3-16).

The normal blood volume within the pulmonary circulation represents approximately 10-12% of the total blood volume, i.e. about 500 – 600 ml. This volume is highly dependent on the intrathoracic pressures; it may be reduced by 50% during substantial increases in the airway- and intrathoracic pressures (e.g. during a Valsalva maneuver), and increased by 100% during forced inspiration (56).

The augmentation of negative intrathoracic pressure during a normal inspiration also increases the blood volume capacity of the pulmonary vascular bed. If the capacity increase in the pulmonary vascular bed during inspiration *surpasses* the increase in RV output due to its increased preload, the increased stroke volume of the right ventricle is not transmitted *directly* to the left atrium; on the contrary, the preload of the LV , and thus the C.O., may *decrease* (fig. 3-16).

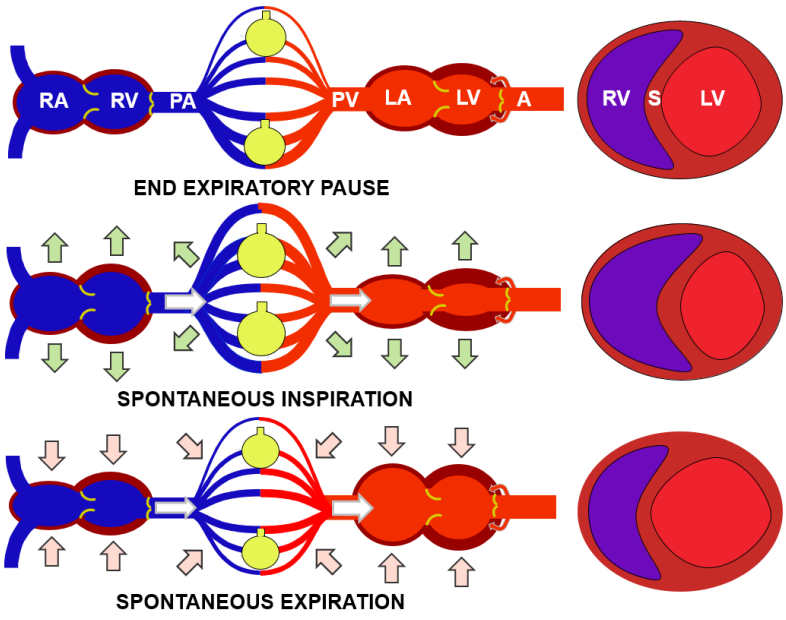

Figure 3-16. *Effects of spontaneous ventilation on the blood volume capacity of the pulmonary circulation, and the consequences for the stroke volumes of the right (RV) and left (LV) ventricle. Size of white arrows indicate magnitude of flow during diastole, see fig 3-1 for abbreviations.*

During expiration, the intrathoracic pressure gradually becomes less negative. The capacity of the pulmonary vascular bed again decreases, and more blood is squeezed from the pulmonary vessels into the left atrium and to the left ventricle. The preload of the LV increases, resulting in a higher SV and increased ABP.

The effects on ABP during a ventilation cycle when breathing normal tidal volumes are of modest magnitude. During *deep* spontaneous ventilations, however, a tidal volume of 1 500 ml results in an LV stroke volume reduction of approximately

30% at end inspiration (57). Hypovolemia accentuates the effect of deep spontaneous breathing on blood pressure variations (58). The effects of both spontaneous and positive pressure ventilation (below) on the circulation may be minuscule, however, in patients with diastolic dysfunction (Part 3-2), or in situations where the filling volumes already are close to optimal. In patients with chronic lung diseases (Part 4-3), the vessels of the lung may be less compliant, and the effects of ventilation on the stroke volumes are less marked.

Positive pressure ventilation and preload.

The above effects are reversed during positive pressure ventilation. The pressure around the pulmonary vessels increases during inspiration; more blood is then squeezed into the LV, increasing the LVEDV and thus the SV and systolic arterial pressure. During expiration, when the intrathoracic pressure falls, the vessels dilate and accommodate a larger blood volume, reducing the LVEDV and thus the systolic pressure. Analogous to that for spontaneous ventilation, these effects are less pronounced (or may disappear) when the diastolic filling volumes are high, or when the compliance of the lung vessels is reduced.

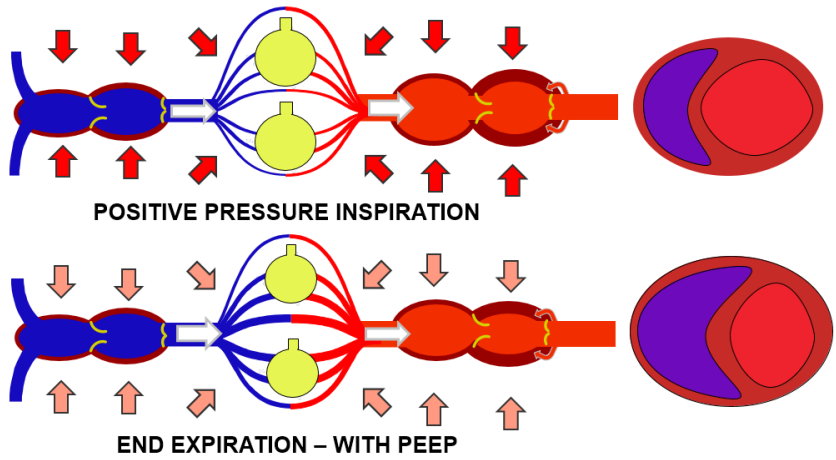

Figure 3-17. *Effect of positive pressure ventilation on intrathoracic pressures and LV afterload in persons with normal lungs and cardiac function during diastole. See fig 3-16 for symbols.*

The pressure within the airways during positive pressure ventilation expands the lungs and *increases* the mean intrathoracic pressure. This pressure then opposes the hydrostatic pressures inside the intrathoracic veins and the chambers of the heart, decreasing the trans-vascular and -cardiac pressures. To maintain a similar transmural pressure as that during spontaneous ventilation, the left ventricular diastolic filling pressures must increase to the same extent as the increase in mean intrathoracic pressure. If not, the end-diastolic ventricular volume (and thus the stroke volume, fig. 3-11 and fig. 3-17) decreases, with the SV being largest during the inspiratory phase (see also review by Pinsky (59).

THE SYSTEMIC ARTERIAL PRESSURE (ABP)

The arterial pressure (**ABP**) is a function of the

- **Left ventricular stroke volume**,
- **Resistance** *and* **elasticity of the vascular bed**,
- **Heart rate**.

The arterial pressure wave and its relation to the cardiac cycle and left ventricular pressures are shown in fig. 3-4. If the total resistance to ejection (impedance, see above) of the vascular bed remains unchanged, variations in SV change the systolic ABP in the same direction.

The **Systolic blood pressure rises** with

- **Increasing stroke volume**,
- **Increasing total resistance** of the systemic vascular bed *and/or*
- **Reduced elasticity of the larger arteries.**

Conversely, it decreases with reduced stroke volume, high elasticity, low vascular resistance and reduced blood viscosity. The effect of **heart rate**, which theoretically should increase the pressure, depends on the rate increase, as very high rates may lead to reduced stroke volumes.

The systolic arterial pressure may remain unchanged if a stroke volume increase is matched by a corresponding reduction in vascular resistance or *vice versa.* In addition, the heart rate influences the peak arterial pressure as the diastolic pressure, before the start of the ejection phase, may be reduced in bradycardia. The blood pressure *per se*, although a crucial factor for the tissue perfusion pressure, is therefore an unreliable surrogate for blood flow to the organism (see below).

The **pulse pressure (PP),** i.e. the difference between systolic and diastolic arterial pressure (see also fig. 3-4), is mainly a function of SV and vascular compliance, with vascular resistance playing the smaller role. The **average**, or **mean arterial pressure**, is referred to as **MAP,** and is calculated as diastolic pressure + 1/3 of the pulse pressure. Most modern electronic measuring devices calculate MAP automatically. The MAP is an important factor in the calculation of various hemodynamic parameters (see below). Even if MAP is an imprecise surrogate for blood flow it is often used to indicate the boundaries of acceptable blood pressure levels in acute- and emergency medicine, anesthesia, and critical care.

The measurement of blood pressure is in itself subject to several variations and inaccuracies. In general, the pressure is higher when lying down than when sitting or standing (60). When it is measured with an inflatable cuff, systolic pressures are generally underestimated and the diastolic pressures are overestimated (61). The dimensions of the cuff must be commensurate with those of the upper arm; in very skinny, obese, or edematous persons, there is a high risk of incorrect measurement. Patients with a central arterial stenosis may also have different blood pressure in each arm, in patients with coarctation of the aorta, the arterial pressure in the lower part of the body may be significantly lower than in the upper (62).

Blood pressure measured invasively, with intra-arterial cannulas and transducers, is also subject to variations. Under normal circumstances, the more peripheral arteries have greater pulse pressure (higher systole) and narrower peak pressure waves than those found in central aortic measurements (63). Systolic pressures in the radial artery are generally higher, and the diastole slightly lower (fig. 3-4) than in the aorta or other more central arteries (64, 65).

In patients receiving infusions of vasoconstricting substances (e.g. adrenaline, noradrenaline, vasopressin) in the course of therapy for circulatory failure, drug-induced contraction of peripheral arteries cause pressures measured in these arteries (often in the radial artery) to be considerably lower than those measured more centrally (femoral artery, axillary artery) (66). Such phenomena are easily seen in tracings from patients treated with an intra-aortic balloon pump, IABP, when the blood pressure is measured simultaneously in the upper part of the descending aorta and often also simultaneously in the radial artery (fig. 3-4).

Relationship between pressure, flow, and vascular resistance.

The relationship between blood flow (**Q**) through an organ, the perfusion pressure (**P**) (i.e. arterial minus venous pressure), and the resistance to blood flow (**R**) is adapted from the laws describing the flow of electricity (Ohms law) and is written as

$$\mathbf{Q} = \frac{\mathbf{P}}{\mathbf{R}}$$

i.e. if the vascular resistance increases, the perfusion pressure must increase proportionally to maintain a constant flow.

If solved for perfusion pressure:

P = Q x **R,**

i.e. the pressure remains constant if a change in either flow or resistance is accompanied by an inverse fractional change in the other factor. If the flow is reduced to 2/3 of normal, a 50% increase in resistance (3/2 of normal) results in an unchanged pressure (see also below).

The systemic vascular resistance (SVR) and arterial blood pressure.

If solved for resistance, it equation above becomes

$$\mathbf{R} = \frac{\mathbf{P}}{\mathbf{Q}}$$

When the equation is applied to the systemic circulation in general (see fig. 3-18), the blood flow (**Q**) is identical to the **cardiac output (C.O.)**. The average perfusion pressure **P** in the systemic circuit is represented by the mean blood pressure (**MAP**), minus the central venous pressure (**CVP**), and **R** is the **systemic vascular resistance** (**SVR).** The sum of **forces that oppose ejection** of the stroke volumes from the LV consists of the *resistance* created by the contractile status of the arterioles, the *elasticity* of the aorta and major arteries (67), and the *viscosity* of the blood, and other factors (see Impedance above). For simplicity, and to comply with common nomenclature in acute and critical care medicine, all these factors are lumped together as the total **systemic vascular resistance** (**SVR)** in the calculations shown below (see also Apx).

When solved for SVR, the equation may then be re-written as

$$\frac{\mathbf{MAP} - \mathbf{CVP}}{\mathbf{C.O.}} = \mathbf{SVR}$$

(see Apx for units used for vascular resistance). If the MAP is low and CVP high (e.g. RV*or* biventricular failure), both pressures must be included for accurate calculation of the vascular resistance. At normal MAP (90-100 mmHg in adults) and CVP (4- 6 mmHg), however, the venous pressure represents such a small factor that the perfusion pressure of the entire body (**P**), *for bedside level of precision* , may be assumed to be equal to **MAP** without great loss of accuracy.

When CVP is in the normal range, a simplified equation can then be used to illustrate the relationship between MAP, C.O. and SVR:

MAP = C.O. x SVR.

This offers a *qualitative* assessment of the circulatory condition; the *quantitative* precision when using this simplification decreases in conditions with reduced MAP and increased CVP (e.g. cardiogenic shock).

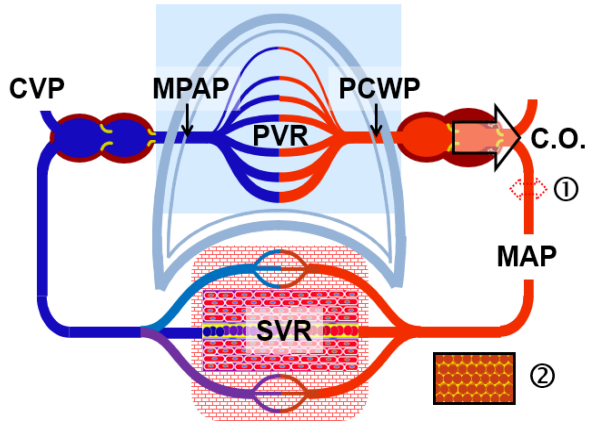

Figure 3-18. *Relationship between vascular resistance, arterial pressure and cardiac output. The elastic properties of the large vessels ① and the blood viscosity ② also contribute to the forces opposing ventricular ejection. See text for abbreviations.*

Arterial blood pressure is easy to measure and represents, in *most* clinical situations (together with other clinical signs, see below), an *indirect* indicator of the LV pumping capacity (i.e. the stroke volume) of the heart.

In some groups of patients, however, arterial pressure is a poor and sometimes misleading indicator of the C.O. (and thus of the circulatory element of DO_2). This can be illustrated by applying the simplified equation above to two patients presenting with the same MAP but widely different C.O. and thus DO_2. Patient **A** has a critically *low* C.O. *and severe vasoconstriction*, patient **B** has a hyperdynamic circulation with a C.O. three times *higher than A* and *substantial vasodilation*. In the calculation example below, the C.O. of **Patient A** is reduced to 2/3 (67%) of normal (e.g. acute cardiac failure, hypovolemic shock), with a 50% compensatory increase (3/2 of normal) in vascular resistance. **Patient B** has a doubled C.O. (100% increase) and a resistance reduced to half (50%) of normal (e.g. severe sepsis or a post-traumatic state in which a combination of intravenous fluids, low afterload, and catecholamine support have optimized cardiac function).

If we multiply each of the terms in the equation above with the change expressed as a *fraction* of *normal* values for C.O. and SVR (**green**), we get an identical MAP for both patients

A (C.O. x 2/3) x (SVR x 3/2) ⇒ MAP ⇐ (C.O. x 2) x (SVR x 1/2) B

As the DO_2 to the organs of the body depends on blood flow and not on pressure *per se*, the C.O. is of more interest than blood pressure in the context of oxygen supply to the body as a whole. In most patients, blood pressures above those necessary to secure adequate organ perfusion pressure offer no advantage as to oxygenation but may represent a strain on the heart and cause increased bleeding in trauma. If, however, localized tissue edema, vascular stenosis, etc. represent an increased resistance to tissue perfusion, additional focus on perfusion pressure to the organs at risk is mandated.

As illustrated by the example above, the **cause of low blood pressure** may roughly be divided into two main types, of which both may co-exist in some groups of patients with severe hypotension (e.g. septic shock, Part 3-3).

i) **Reduced cardiac output** (hypovolemia, venous vasodilation, primary heart failure, etc.). In such patients, the severity of hypotension reflects the degree of tissue hypoxia and shock in a non-linear fashion.

ii) **Low vascular resistance,** due to **pathological (or therapeutic) arteriolar vasodilation** and/or **reduced blood viscosity.** In such patients, the blood flow to the organism as a whole may be normal or even supernormal (warm shock).

Severe hypotension does not *necessarily* indicate tissue hypoxia; as long as an adequate preload, and thus C.O., is maintained, tissue perfusion may be adequate (Part 3-3, Hypotension in the vasodilated patient). If unexplained, it is a sign of danger.

The pulmonary vascular resistance (PVR) (see also Part 4-1).

The perfusion pressure of the pulmonary vascular bed is the mean pulmonary arterial pressure (**MPAP**) minus the mean left atrial pressure (usually measured as the pulmonary capillary wedge pressure – **PCWP,** also termed pulmonary artery occlusion pressure **- PAOP**) see fig. 3-18. A high PAP increases the workload on the right ventricle and may induce RV dilatation, hypertrophy, and failure. The MPAP is usually calculated as the *middle* value between systolic and diastolic pressures. The relationship in the pulmonary vascular bed may then be written

MPAP – PCWP = C.O. x PVR

The normal difference between MPAP and PCWP is small (typically in the 7-12 mmHg range), ignoring the left atrial pressure when calculating the PVR cause errors of an unacceptable magnitude. For reasonably accuracy, both pressures *must* be entered into the equation:

$$\frac{(\mathbf{MPAP} - \mathbf{PCWP})}{\mathbf{C.O.}} = \mathbf{PVR}$$

C.O. can be measured by several methods (Part 3-4); approximate MPAP and PCWP values can be estimated by the echo-doppler cardiography technique but *accurate* bedside measurements of both parameters requires a PA catheter (Part 3-4, PA catheter). Reliable estimates of the PVR, therefore, require the insertion of such a catheter. A table of "normal" hemodynamic values (table 3-1) is shown at the end of this Part.

THE RESERVE CAPACITY OF THE NORMAL HEART

Increased C.O. can, fully or in part, compensate for an **increase in O_2 demand** (i.e. augmented O_2 consumption ($\dot{V}O_2$), or a **decrease in arterial O_2 content.**

The normal heart can increase its pumping capacity 3 to 4 times, as illustrated by the C.O. response to increased $\dot{V}O_2$ during strenuous muscular exertion (see fig. 3-19). In most investigations of this type (except for those carried out at high altitudes, where the Hb usually is increased), the O_2 content of the blood (C_aO_2) is normal.

The cardiac response to acute reductions in C_aO_2 (e.g. anemia, hypoxemia) *may* ensure that the O_2 delivery (DO_2), although reduced, remains sufficient to cover the $\dot{V}O_2$. During *severe* reductions in C_aO_2, however, the blood perfusing the myocardium may not be able to deliver the quantity of O_2 necessary to mount an efficient cardiac response in the form of increased pumping capacity. The circulatory compensatory response may then be blunted or abolished.

Increased O_2 demand is also accompanied by an **increased extraction of O_2 from the blood** (i.e. increased difference between the O_2 content of C_aO_2 minus $C_{\bar{v}}O_2$). For simplicity, the SO_2 in blood from a central venous catheter is often used as a surrogate marker for changes in the O_2 extraction fraction (OEF) and thus in the $DO_2/\dot{V}O_2$ ratio. The accuracy of this practice is, however, poor if not corrected for the C_aO_2 (Part 3-4 and Part 5-4).

Increasing the C.O. in response to increased $\dot{V}O_2$.

Even moderate physical exertion in non-athletes elicits an almost 100% increase in C.O. (68). In healthy non-athletes participating in scientific investigations of cardiac response, the C_aO_2 of the

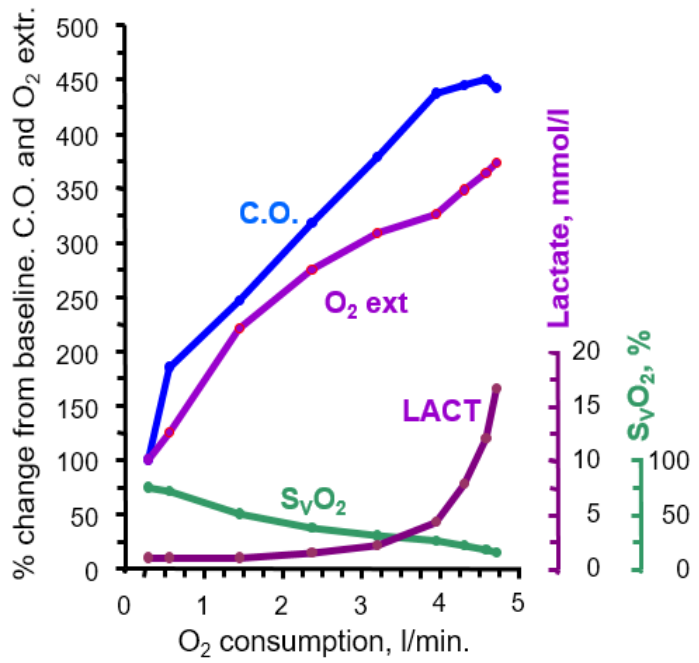

Figure 3-19. *Changes in C.O. (blue) and O_2 extraction (lilac) as a function of $\dot{V}O_2$ during increasing strenuous exertion in well trained subjects, data shown as % of assumed resting values (left Y-axis). Also shown are simultaneous changes in S_VO_2 (green) and lactate (plum), as absolute values (right Y-axes). Curves are based on data from ref 48 with assumed normal resting values as the baseline.*

blood is usually normal; in athletes, it is often supernormal due to higher Hb levels. The O_2 supply to the myocardium is then limited only by the flow rate through the coronary circulation. Maximal exertion in highly trained athletes increases the C.O. to between three (48) and five (69) times normal, depending on experimental conditions and duration; individual peak values as high as 42.3 l/min have been reported (69).

As the maximal O_2 uptake increases 10-fold or more during strenuous exercise (49, 70), increased extraction of O_2 is also necessary to fulfill the aerobic requirement of the muscles. During maximal exertion for limited periods, the O_2 extraction may increase by a factor of about 3.5 above baseline, reducing the O_2 saturation in mixed venous blood (S_VO_2) from the normal resting value of about 75% down to about 12% (48), see fig. 3-19.

The C.O. increase at maximal exertion is due to a combination of approximately two- to three-fold increase in HR (to about 180/min) combined with an increase in stroke volume of close to 30% (48) or more (68). In non-athletes, the pattern is similar to that in athletes; the SV of non-athletes is smaller, but increases by approximately the same percentage; the peak HR increase in athletes and non-athletes is similar (68). The increases in stroke volume of non-athletes show, however, large individual variations. During heavy exercise, the SV increase in assumedly healthy volunteers between 20 and 50 years of age was found to vary from 2% to 70% (4).

THE CAPACITY FOR INCREASING C.O. IN RESPONSE TO REDUCED C_aO_2.

The effect of anemia on C.O. and O_2 extraction.

In anemia, the reduction in C_aO_2 is *almost* linear relative to the reduction in Hb (Part 2-3). This also affects the O_2 supply to the heart; in healthy individuals, the capacity of the cardiac circulation to dilate and thus increase the blood flow is huge. In a non-critical reduction of C_aO_2 due to anemia, the myocardial O_2 supply is therefore well preserved and the reduced C_aO_2 induces a positive cardiac response.

Under experimental conditions, an acute decrease in Hb to about 40% of the initial value (from mean 12.5 g/dl to 4.8 g/dl), without a change in blood volume, triggers a spontaneous mean increase in C.O. to about 80% above baseline in healthy, normovolemic volunteers (fig. 3-20). This is far below the maximal increase in strenuous exercise (fig. 3-19) and lower than during

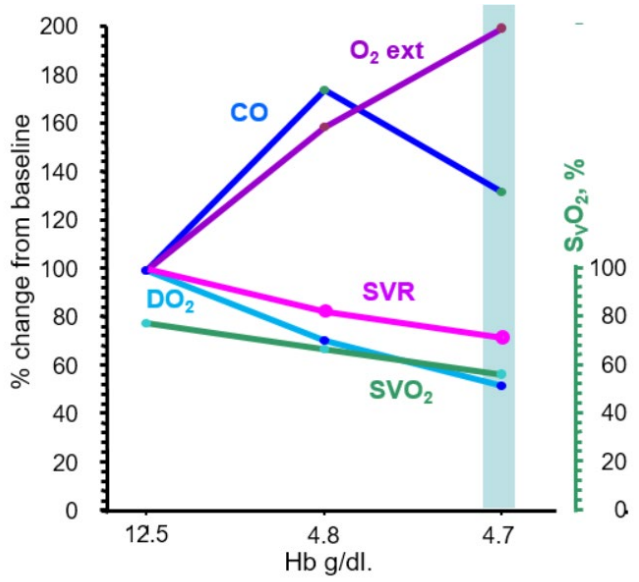

Figure 3-20. *Changes in C.O. (blue), O_2 extraction (lilac), O_2 delivery (light blue) and systemic vascular resistance SVR (light red) in percentage of baseline after euvolemic reduction of Hb in healthy volunteers. S_VO_2 (green) is shown in absolute values (right Y-axis). Points within the blue-green rectangle show the effect of inhibiting the cardiac response with a beta blocker. Based on data presented in ref 71.*

exercise in non-athletes (see above); the substantial reduction in Hb may limit the cardiac response by reducing the myocardial O_2 supply. At the same time, the mean O_2 extraction increased by close to 60% (71). In such settings, the C.O. increase is mainly due to about a 60% increase in heart rate, supplemented with about a 20% increase in stroke volume (50). If the increase in C.O. was attenuated by the administration of a beta-blocker, the O_2 extraction rose to about 200% of normal.

The effect of hypoxemia due to low F_IO_2 on C.O.

An acute reduction in S_aO_2 by about 17% (to a S_aO_2 of approximately 80%) in healthy volunteers elicited only a 20% increase in C.O. (51). The C.O. increase was entirely due to an increase in heart rate, the lack of stroke volume increase may be due to a negative effect of hypoxemia on the myocardium, reducing the diastolic filling despite vasodilation of the coronary vessels (72). At simulated high altitudes where the S_aO_2 was reduced to close to 50%, the stroke volume of well-trained volunteers *decreased* while the ability to mount an increase in heart rate was preserved (73). The observed hypoxia-induced increase in pulmonary arterial pressures to three times baseline, increasing the RV afterload, probably also contributes to a more modest C.O. increase in experiments where hypoxemia is created by breathing gas with a low PO_2 (Part 4-1).

Thus, the C.O. response to acute reductions in C_aO_2 seems to be better preserved in anemia than during hypoxemia at real or simulated very high altitudes. This is supported also by animal experiments, where the C.O. of anesthetized dogs in one study increased by approx. 40% in response to graded reductions in DO_2 if the reduction was due to reduced Hb, but fell by approximately 17% if a similar C_aO_2 reduction was due to a reduction in SO_2 (74).

Failure of adequate cardiac compensation for reductions in C_aO_2.

Regardless of the magnitude of changes in C_aO_2 and/or $\dot{V}O_2$, *or* the level of training, a compensatory increase in C.O. may be blunted or abolished if the diastolic filling is insufficient (e.g. hypovolemia, acute venous vasodilation, increased intrathoracic- or pericardial pressures, diastolic dysfunction, etc. see Part 3-2). The C.O. response may also be compromised by various other causes, *independent* of the diastolic filling (e.g. ischemic cardiac disease, post-ischemic states, septic- drug- or toxic effects, chronic heart failure, valvular disease, conduction disturbances, etc.).

Hemodynamic parameters

MEASURED

Parameter	Normal range	Units
ABP Syst	90-140	mmHg
ABP Diast	60-90	mmHg
MAP	70-105	mmHg
CVP	2-6	mmHg
PAP Syst	15-25	mmHg
PAP Diast	8-15	mmHg
MPAP	10-20	mmHg
PAOP (LAP)	6-12	mmHg
C.O.	4-8	l/min
CI	2.5-4.0	$l/min/m^2$
HR	60-100	beats/min
SV	70-120	ml/beat
LVEDV	100-180	ml
RVEDV	100-190	ml

CALCULATED

Parameter	Normal range	Units
SVR	800-1200	$dynes \cdot sec/cm^{-5}$
SVR	10.0-15.0	mmHg/l
SVRI	1970-2400	$dynes \cdot sec/cm^{-5}$
PVR	150-250	$dynes \cdot sec/cm^{-5}$
PVR	2.5-3.1	mmHg/l
PVRI	255-285	$dynes \cdot sec/cm^{-5}$
EF	58-76	% (of LVEDV)
LVSWI	50-62	$mmHgxml/m^2$
RVSWI	5-10	$mmHgxml/m^2$

Table 3-1: *Normal range for selected hemodynamic parameters. See text for further explanations. Equations for calculation of derived parameters, as well as explanation of abbreviations, are given in the text. Hemodynamic values changes with body weight, age and sex. Due to the substantial span of "normal" values, some parameters may be within the ranges shown above even in some patients with serious disease.* **PAOP** *(pulmonary artery occlusion pressure) is identical to pulmonary capillary wedge pressure* (**PCWP**) ≈ LVEDP.

3-2. CARDIAC DYSFUNCTION

INTRODUCTION

To ensure the tissue O_2 supply, the heart must be able to adapt to a wide variety of changes in metabolism, the state of peripheral circulation, and the O_2 content of the blood. The ability of the heart to mount an adequate response to changes in

- **Vascular resistance** (systemic *and/or* pulmonary)
- **Venous return** (i.e. RV preload) and/or LV end-diastolic volumes
- **Oxygen consumption** ($\dot{V}O_2$) (e.g. fever, muscular exertion)
- **The oxygen content of the blood** (C_aO_2) (hypoxemia, anemia)

determine the capacity of the organism to cope with diseases, physical and mental stress, as well as environmental changes.

The probability of developing some type of cardiac dysfunction increases with age (75, 76). With the increase in the mean age of the population in the industrialized world, the number of such patients is expanding. Changes in cardiac anatomy and valvular- or myocardial function may reduce the capacity for supplying O_2 to the tissues. Cardiac dysfunction represents a continuum of conditions with a wide range of severity, from a slight reduction in the cardiac reserve capacity with no symptoms during everyday activities (*asymptomatic cardiac failure*) to **heart failure severely limiting daily activities**. In **cardiogenic shock,** the cardiac dysfunction is so severe that the O_2 supply to the tissues can no longer sustain aerobic metabolism in all organs and tissues even at rest; the ultimate circulatory failure is **cardiac arrest**.

In elective settings, the diagnosis and therapy of both acute and chronic cardiac conditions normally fall within the domain of cardiologists. During acute non-cardiac incidents (e.g. serious infections, trauma, burns, hemorrhage), as well as during acute myocardial ischemia episodes, a stable asymptomatic cardiac dysfunction may rapidly change into instable one. If instability progresses to circulatory shock, the responsibility for initial diagnosis and therapy in many instances falls on those most often involved in maintaining the patient's vital functions in prehospital- and other emergency settings (e.g. emergency medical personnel, anesthesiologists and surgeons, intensive care generalists). In large hospitals in the industrialized world, these may have rapid access to consultations with a variety of sub-specialized cardiologists (provided they correctly have identified cardiac dysfunction as a major contributor to the problem). In rural settings, and under conditions where resources are limited, basic understanding of the pathophysiology of circulatory disturbances by non-specialists is of great importance for choosing the right therapeutic strategy.

Acute circulatory failure may also be caused by*extracardiac* mechanisms. In some types of shock (e.g. major arterial hemorrhage, major pulmonary embolism, see below), symptoms of tissue hypoxia may develop within seconds to a few minutes. In such situations, the presence of asymptomatic cardiac failure aggravates the negative effects of hypovolemia, anemia, hypoxemia, infections, etc. on the O_2 delivery to the tissues and thus constitutes an additional threat to the organism.

ACUTE CARDIAC DYSFUNCTION AND FAILURE

The left ventricle in circulatory failure.

The capacity of the **left ventricle** (**LV**) for pumping oxygenated blood into the aorta (i.e. the **C.O.**) determines the O_2 supply the tissues. Reductions in LV capacity may originate **within** the heart *per se* (e.g. *cardiac dysfunction, chronic- or acute heart failure (CHF or AHF,* see below), or be **independent** of the myocardial or mechanical function of the heart (e.g. *insufficient venous return, obstruction of central blood flow*).

Regardless of etiology, a severe reduction in LV pumping capacity results in **acute circulatory failure** or **circulatory shock**. Even if extreme bradycardia *can* result in critically low C.O., acute circulatory failure is usually the result of a **SV reduction** to an extent where an increase in cardiac **frequency** (if mounted) **cannot compensate for the SV reduction**. In this compendium, reduced SV is assumed to be the cause of acute circulatory failure and circulatory shock unless otherwise specified.

Moderate cardiac dysfunction.

In patients with modest or no symptoms in everyday life, functional changes that cause the dysfunction is revealed if the heart fails to cope with additional demands on the circulation. Such dysfunction may be envisioned as an **early stage** of **heart failure (HF)**, designated "asymptomatic left ventricular dysfunction" - ALVD (77). Patients with diabetes seem to be particularly at risk for developing this condition (78).

Although many of these patients do not have a heart failure diagnosis, their hearts may not respond to increased O_2 demands or to therapy in the same way as healthy hearts (see also Part 3-3). This may be one of the most important reasons why many older patients, not previously diagnosed with HF, fail to cope with circulatory changes induced by trauma (79) and other serious diseases of non-cardiac origin (80). Especially in patients with diastolic dysfunction, the Frank-Starling mechanism is attenuated or lost. The optimal preload may be challenging to predict in such patients (81); the cardiac response to fluid infusions is thus difficult to determine. Cardiac dysfunction may be primarily systolic *or* diastolic (see below, fig. 3-21 and 3-22), or a combination of both.

Heart Failure (HF).

When cardiac dysfunction reaches a level where even modest increases in daily activity result in symptoms of cardiac decompensation, or the patient experiences symptoms even at rest, the patient is in **heart failure**. The condition is currently defined as "a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress" (82).

The term **heart failure** is not very precise; it is used to describe a wide range of states, spanning from **moderate cardiac dysfunction** (see asymptomatic heart failure above) to **severe circulatory failure of cardiac origin** (cardiogenic shock, see below). In chronic heart failure (**CHF**), a C.O. adequate for the necessary DO_2 can usually be maintained at rest. The cardiac reserves are, however, limited and even moderate increases in $\dot{V}O_2$ or changes in fluid balance

(i.e. increased or reduced filling pressures) can precipitate acute symptoms like orthopnea/dyspnea (i.e. incipient pulmonary edema) and peripheral edema.

A system for **classifications of the severity of heart failure**, dividing the functional state of a patient into four groups, was developed by the New York Heart Association (**NYHA)** (83).
The states are
I. No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
II. Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, and dyspnea (shortness of breath).
III. Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV. Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Classes **III** and **IV** represent **severe HF**; determining whether persons in class I should be classified as having HF *or* slight cardiac dysfunction may be difficult and depend on individual experience and judgment.

Most patients with HF have high LV filling pressures and -volumes; when in a stable, compensated phase, continuous stimulation of baroreceptors and release of catecholamines to maintain the ABP may result in a chronically *constricted systemic vascular bed* and a *reduced blood volume* (84). Such patients tolerate an acute reduction of blood volume (hemorrhage) poorly; they are also more sensitive to the vasodilation induced by central nerve blocks and the actions of vasodilating agents and drugs.

More than 40% of patients with chronic heart failure have some degree of diastolic dysfunction (see below) with a preserved ejection fraction, i.e. normal or reduced end-diastolic volume but normal contractility (**H**eart **F**ailure with **p**reserved **E**jection **F**raction - **HFpEF**). The rest often have dilated hearts with a reduced ejection fraction (**H**eart **F**ailure with **r**educed **E**jection **F**raction - **HFrEF**) (85, 86). The former group needs an increased LV filling pressure to obtain a close to normal LV filling volume (87); the degree of diastolic LV pressure increase that can be tolerated is, however, limited by the risk of developing hydrostatic pulmonary edema (see figs 3-21 and 3-22, also Part 4-3). As increasing the preload requires high filling pressures; patients with diastolic failure gain little benefit from the Frank-Starling mechanism. In these patients, measurement of LV end-diastolic *pressure* (the filling pressure) may indicate whether there is a of danger of pulmonary edema formation, but the pressure represents a poor, and often misleading, surrogate indicator of the filling volume (i.e. the *true preload*) of the heart.

Circulatory failure as a result of left ventricular dysfunction.

LV dysfunction may be acute or chronic; the *initial* etiologic mechanisms can be roughly grouped into

- **Myocardial** dysfunction, manifesting as systolic *or* diastolic dysfunction (see below) of the cardiac chamber walls, or a combination of both. Dysfunction usually develops secondary to ischemia, hypertension, defective valves, etc. *but* may also be induced by non-cardiac diseases, drugs, and toxins. In rare instances, the dysfunction may be inherited (congenital dysfunction).
- **Mechanical** dysfunction, where the myocardium in the initial phase contracts normally but where mechanical constraints *or* cardiac valve- *or* septum defects reduce the volume of blood

pumped into the aorta. Such defects may change the geometry of the ventricles and the myocardial mass over time, which again changes the functional properties of the LV.

- **Node-** and/or **conduction** dysfunction, where the myocardial cells initially have normal contractility but where defective impulse generation and/or abnormal conduction pathways inhibit synchronized contraction of the chambers. Such asynchrony reduces the heart's ability to generate sufficient output in response to increased O_2 demands.

As one type of dysfunction over time may induce additional types, any combination of the above may be present. Cardiac dysfunction may progress to acute circulatory failure if additional episodes of myocardial ischemia, mechanical insults or arrhythmias, etc. occur, *or* when the heart is faced with increased $\dot{V}O_2$ *and/or* decreased C_aO_2 that place additional demands on the circulation.

Acute heart failure (AHF).

Acute heart failure (AHF) refers to the rapid onset or worsening of symptoms and/or signs of HF. It is a life-threatening medical condition requiring urgent evaluation and treatment (75). If occurring suddenly in persons previously assumed to be in good health, the most common cause is *myocardial ischemia*. Major *pulmonary embolism* is a rarer cause, but may initially present with similar symptoms (Part 3-3). Drugs or toxins, infectious or traumatic damage to valves, myocarditis, etc. may also cause acute failure. In addition, it may present as an acute exacerbation (due to additional stress, myocardial ischemia, etc.) of known chronic diseases of the heart (CHF) and/or the circulation.

The most dramatic examples of AHF are

- **Cardiogenic shock**, where the pump function of the beating heart fails to maintain a blood flow compatible with generalized aerobic metabolism even at rest.
- **Cardiac arrest**, where circulation ceases within seconds, and external chest compression (or internal cardiac compression) are the only options for survival until spontaneous cardiac activity (ROSC) occurs *or* maintenance of circulation by invasive mechanical means can be established (Part 3-4).

Systolic and diastolic dysfunction of the left ventricle.

Independent of whether the circulatory failure is due to acute or chronic cardiac conditions, a reduced stroke volume may be due to either systolic **(**fig. 3-21) or diastolic **(**fig. 3-22) dysfunc-tion, or a combination of both. In patients with primarily diastolic dysfunction, aggressive fluid therapy may have a negative effect on the DO_2 (by increasing the risk of pulmonary edema and thus reduce the C_aO_2 with little or no benefits on cardiac output). Identification of such dysfunction in patients with clinical circulatory failure is therefore of great importance for the choice of therapeutic strategies.

Systolic dysfunction is the most common cause of impairment of the functional reserve of the left ventricle (fig. 3-21); the reduction in myocardial contractile force (or in the mass of functional myocardium after infarction) leads to the ejection of diminished stroke volumes. These patients often have an increased left ventricular end-diastolic filling volume (LVEDV) and may have exhausted the benefits of increased preload (the Frank-Starling effect) while the calculated EF (see fig. 3-3) is reduced.

Diastolic dysfunction is less common as a cause of acute failure, but is a more common cause of chronic dysfunction than previously assumed. When the diastolic relaxation is impeded (i.e. a

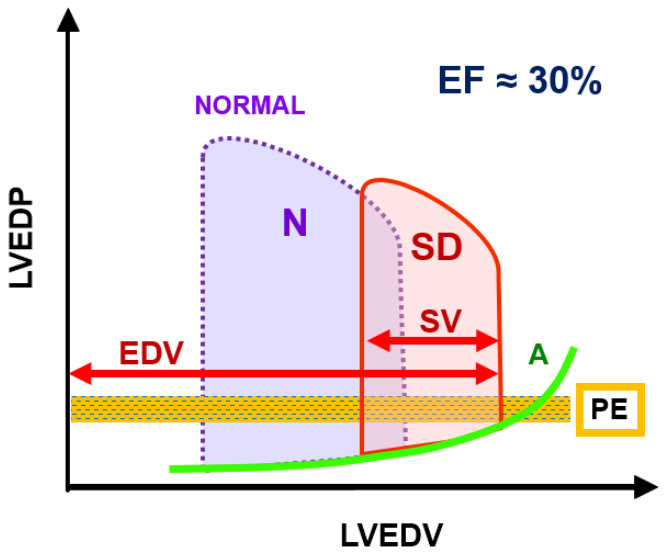

Figure 3-21. *Pressure-volume loops for normal LV* (N) *and for a LV with* ***systolic dysfunction*** (**SD**) *and chronic dilatation of the heart, but following a normal end-diastolic pressure-volume curve* (**A**). *If the SV is reduced by ≈ 30%, the EF is reduced to ≈ 30%.* **PE**: *L V pressures when pulmonary edema may be expected to occur.*

less compliant, "stiffer" myocardium, often associated with myocardial hypertrophy or fibrosis); the curve describing the relationship between filling volume and filling pressure is much steeper than normal (curve B in fig. 3-22). This diminishes the diastolic filling volume of the heart at a given filling pressure (reduced **preload**), while the contractile force of the left ventricle is maintained. Small filling volumes lead, however, to small stroke volumes; the calculated EF may therefore be relatively normal.

As systolic dysfunction is the most common condition in HF, it has traditionally received most attention from both cardiologists and physicians involved in acute and critical care (88); HF was in most instances considered to be caused by a systolic failure (89). Diastolic failure was first described as a separate disease in 1937 (90). During the last four to five decades, however, there has been an increasing realization that diastolic dysfunction is more common than previously assumed. Of clinical importance is that an increasing number of older persons develop such cardiac dysfunction, which seriously may impair their cardiac reserve, without having overt symptoms of heart failure (10). Much of the research concerning human circulatory failure and indications for therapeutic interventions like infusions of fluid and inotropes have been carried out in ICUs, where attempts at circulatory stabilization have already been implemented, and the mean age of patients enrolled in many studies is above 60 years (91, 92). Previously undiagnosed diastolic cardiac failure may have a high incidence in such populations; the conclusions derived from such studies may therefore not be valid for treatment of younger patients with essentially normal cardio-circulatory function (e.g. civilian trauma, combat trauma).

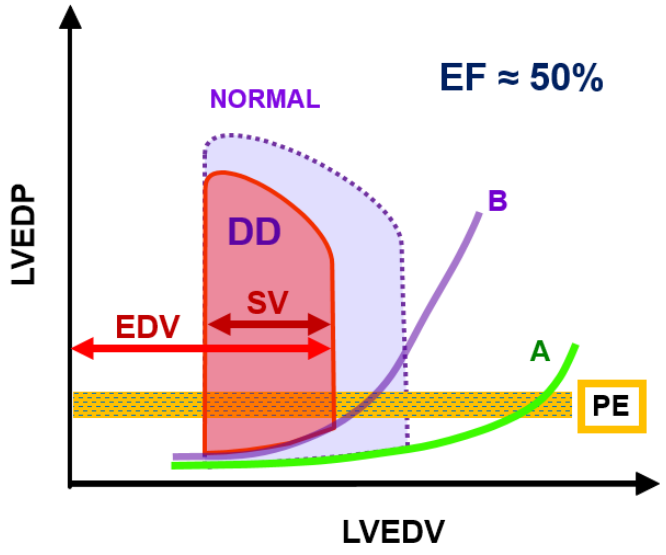

Figure 3-22. *Pressure-volume loops for normal LV, and for LV with* ***diastolic dysfunction*** *with* (**DD**) *creating an abnormal end-diastolic pressure-volume curve* (**B**) *The SV is reduced by ≈ 30% (as in 3-21); due to the reduced LVEDV, however, the EF is preserved in the normal range (50%). Increasing filling pressures to augment the preload may precipitate pulmonary edema* (**PE**) *– see also fig 3-21* .

The subdivision of patients into those with a primarily **systolic** (93) or **diastolic** (94) dysfunction has huge consequences for both diagnostic considerations and the expected effect of therapeutic interventions. The cardiac pump function of most patients with **systolic dysfunction** benefits from drugs that **enhance myocardial contractility** and/or **reduce vascular resistance**, while such treatment has minimal or no beneficial effect on those where diastolic dysfunction is predominant (95). Figs 3-21 and 3-22 show the principal difference between isolated systolic and diastolic dysfunction in hearts with equal stroke volumes. In acute myocardial ischemia, diastolic and systolic failure may occur simultaneously (96).

ETIOLOGIES OF LEFT VENTRICULAR MYOCARDIAL DYSFUNCTION.

The etiologies of LV myocardial dysfunction may roughly be divided into

- **Ischemic** (chronic, but *without* infarction, *or* acute, *resulting in infarction* with permanent loss of functional myocardium).
- **Acquired hypertrophy** (remodeling of the ventricular wall in response to increased *stretch* (increased volume) or *workload* (increased afterload)).
- **Cardiomyopathies** (primarily genetic, or secondary to other diseases).

Ischemic dysfunction may be **reversible** (stunning, hibernation**)** or **irreversible** (myocardial death) if re-oxygenation of the affected tissue cannot be established.

Reversible dysfunction.

Myocardial stunning may occur when acute myocardial ischemia is followed by reperfusion within minutes to a few hours; the *permanent* myocardial damage may be modest but cardiac function can be *severely reduced* during the initial *post-ischemic phase.* The reduction in myocardial contractility may last for several hours to a few days after reperfusion, but a close to normal function is usually re-established if further episodes of myocardial hypoperfusion can be avoided. This state is mostly seen after cardiac surgery or angioplasty; if revascularization has been successful, the use of positive inotropic agents do not represent the same danger of myocardial ischemia as in patients with coronary vascular occlusion.

Myocardial hibernation is a state of potentially reversible myocardial dysfunction (reduced contractility) that can last for months to years. Chronic hypoperfusion of the myocardium is assumed to be the underlying cause; myocardial function improves after interventions that increase the myocardial perfusion (97).

Irreversible dysfunction.

The most common cause of acute LV dysfunction is insufficient O_2 supply due to localized perfusion deficits in part of the myocardial wall (myocardial ischemia). **Myocardial infarction** results if the ischemic area is not re-vascularized within a few hours. In controlled animal experiments with temporary coronary artery occlusion, all the myocardial tissue survives if reperfusion starts within 15 min but dies if reperfusion is delayed by more than 60 min (98). Myocardial reperfusion in humans is, however, clearly beneficial even if reperfusion is delayed for up to 2 hours or even more after the initial symptoms of vascular occlusion (99), see also Part 3-3.

If not reperfused, the affected myocardium becomes necrotic and is eventually replaced by non-contracting scar tissue. Until the fibrotic process is complete, a full-thickness necrotic myocardial tissue area represents a weak spot in the chamber wall and may lead to rupture of the ventricular septum or the outer wall of the ventricle, with rapid development of cardiogenic shock.

The consequences of myocardial infarction for LV function depend on the localization and the size of the area of the damaged myocardium. The larger the scar area, the more work the undamaged myocardium must perform to keep the stroke volumes normal. This may lead to post-infarction **remodeling** of the LV, with asymmetric hypertrophy of the remaining myocardium. If the infarcted area involves major parts of the *conduction* system, arrhythmias may compound the negative effects of the loss of contractile tissue and, in the worst case, progress to life-threatening arrhythmias. The risk of dangerous arrhythmias is greatest during the first 2 days after an infarction (100).

Myocardial infarction may be silent (i.e. occur without symptoms normally associated with infarction, or with no symptoms at all) in more than 25% of persons found to have suffered a myocardial infarction by routine examination (101); the percentage of females with silent myocardial infarction is greater than in men. Changes in LV function occur within a few seconds after the onset of myocardial ischemia, while angina symptoms may be delayed for a minute and more (102).

Non-ischemic remodeling of the ventricles.

In response to chronic increases in right or left ventricular afterload (e.g. systemic- or pulmonary hypertension, aortic or pulmonary valve stenosis) and/or chronically increased filling volumes (e.g. aortic valve insufficiency, ventricular septum defects), the muscle mass of the myocardium may increase. The hypertrophy of the chamber walls is an adaptive process, analogous to the hypertrophy of skeletal muscles occurring after demanding training regimes where increased strength of skeletal muscle is the goal.

During hypertrophy, the *number* of myocardial muscle fibers stays constant. Two main patterns of hypertrophy are commonly found. One is due to an increase in size in the myocardial cell longitudinal axis (**eccentric hypertrophy)**, in which the thickness of the wall is normal or moderately increased but the end-diastolic volume is increased. The other is due to an increase in the size of the transversal axis (**concentric hypertrophy**) in which the thickness of the wall is increased but the end-diastolic volume is normal or modestly reduced, see fig. 3-23. The former is the most common in chronic volume (preload) overload, and the latter is most common in chronic afterload increase (103).

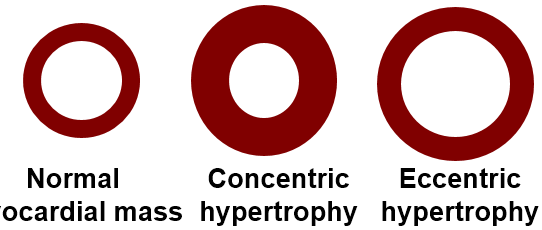

Figure 3-23. *Schematic illustration of concentric and eccentric myocardial hypertrophy.*

Hypertrophy is a physiological adaption mechanism and beneficial during the earlier phase of increased work due to hypertension, *or* mechanical factors that increase the myocardial workload (e.g. valvular disease, septum defects, see below), but can also have negative aspects. The hypertrophy may lead to diastolic dysfunction; as increased myocardial mass consumes more O_2, the danger of ischemia increases if localized obstructions to perfusion increase. In addition, hypertrophy is associated with an increased frequency of arrhythmias (104).

Similar remodeling may be a result of intense training regimes in athletes. Training for increased endurance commonly results in eccentric hypertrophy, and training for increased strength most often results in concentric hypertrophy (105).

Cardiomyopathies

Cardiomyopathy is a state of cardiac dysfunction (most often of LV), where none of the usual etiologic factors, like ischemia, hypertension, valvular disease, etc. are present, or where the myocardial changes are out of proportion to etiologic factors (106). Cardiomyopathies can be **primary** (i.e. genetic or acquired affection of the function of the myocardium *per se*) or **secondary** (i.e. when other diseases, toxic agents or drugs, infections, and inflammatory states or metabolic imbalances exerts a negative effect on myocardial function) (107, 108). Some rarer cardiomyopathies may be an expression of mitochondrial disease (109).

Dilated cardiomyopathy is the most common form of cardiomyopathy, while **hypertrophic cardiomyopathy** is associated with sudden death in athletes (110). Around 20% of all cardiomyopathies may be due to congenital factors (111); the consequences of LV dysfunction caused by genetic factors do not differ from dysfunction due to other, well-known, factors.

MECHANICAL DYSFUNCTION OF THE HEART

Valvular dysfunction.

Dysfunction of valves on the left side of the heart has the gravest consequences, as they are charged with maintaining a *one-way flow* in a high-pressure system. Dysfunction of valves in the low-pressure system on the right side of the heart usually has less dramatic consequences. Changes occurring in valves on the left side will eventually also affect the RV function, as all types of valve dysfunction on the left side of the heart eventually leads to increased pressures in the pulmonary vascular bed and thus increases the RV workload.

In countries with a well-functioning health system, defective valves are usually repaired or substituted (surgically, or by trans-vascular interventions) when they lead to serious symptoms. Some patients, however, may present with previously undiagnosed serious valve dysfunction that becomes evident in connection with other diseases. The hemodynamic consequences of stenosis and insufficiency of the valves are illustrated in figs 3-24 and 3-25.

According to a US study, about 20% of patients admitted to hospitals with heart failure had some kind of valve disease (112). In studies from the UK, valve disease was found to be the main etiologic factor in 7% of patients with heart failure (113); of patients referred to specialists due to clinical suspicion of heart failure, 37.5% had mild valve disease, 11.3% had moderate valve disease and 2.7% had severe valve disease. The most common causes in the severe group were aortic stenosis (1.17%), mitral regurgitation (0.45%), aortic regurgitation (0.19%), and mitral stenosis (0.06%), while a modest degree of mitral regurgitation (9.4%) was most common in the "mild" group (114).

Valvular dysfunction is usually a chronic condition, in which **hypertrophic remodeling** of the myocardium (see above) may compensate for the increased myocardial workload. Such compensation may function well for many years, but ultimately heart failure may develop as the lesion progresses and the person grows older. The consequences of valve dysfunction as to remodeling and ventricular function thus vary with age and stage of the disease.

In **acute valvular dysfunction** (usually in the form of acute valve insufficiency, see below), there has been no time for gradual development of myocardial hypertrophy as a defense mechanism; acute dysfunction is, therefore, less well tolerated. The symptoms resulting from a dysfunctional valve thus do not depend only on the type and degree of dysfunction, but also on whether compensatory myocardial hypertrophy has had sufficient time to develop.

Valvular stenosis.

Stenosis of the *PA and aorta valves* requires augmented work to eject a normal SV and thus represents an increased ventricular *afterload*, a stimulus to ventricle hypertrophy. Stenosis of the *mitral and tricuspid valves* represents a problem with maintaining sufficient ventricular *preload*. Increased atrial pressures are required to maintain a normal atrial-ventricular flow; this leads to atrial dilatation and increased venous pressures. Valvular stenosis is seldom acute, although hyper-acute outflow obstruction in rare instances may be caused by acute dysfunction of artificial valves, impaction of thrombotic material, and intracardiac tumors.

Valvular stenosis may be congenital or acquired, stenosis of the pulmonary or aortic valves (115) is most common. In the industrialized western world, acquired dysfunction is usually a result of degenerative and calcification processes. In developing countries, rheumatic disease, a result of Streptococcus type A infections, is still a common etiology (116). All types of valvular dysfunction represent an increased workload on the heart.

Acute valvular insufficiency.

In opposition to stenosis, valve insufficiency may occur acutely. It may be a result of myocardial infarction (e.g. necrosis of papillary muscle leading to severe mitral regurgitation) or endocarditis (e.g. destructive lesions of the aortic valve), trauma, or dissection of the ascending aorta involving the aortic valve. Acute mitral valve regurgitation or insufficiency (**MI)** may also be a result of LV dilatation (functional MI), in which case it is reversible if treatment aiming at reducing the dilatation is successful. In acute insufficiency, the myocardium is "unprepared" (i.e. no time for development of myocardial hypertrophy) and the consequences of valve insufficiency on cardiac function are more severe.

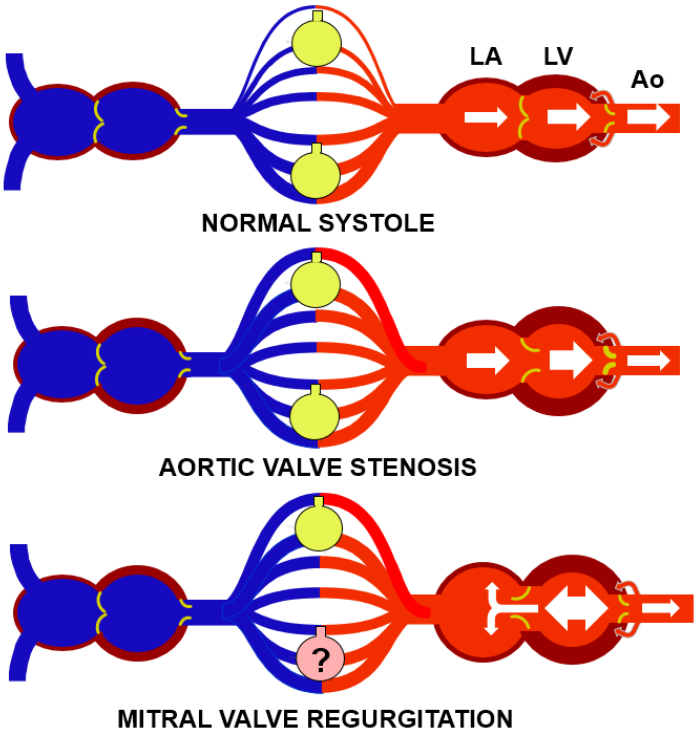

Figure 3-24. *Effects of aortic valve stenosis and mitral valve insufficiency on the stroke volume and workload of the left ventricle. White arrows indicate LA and LV pressures; their size indicate changes from normal. When LA pressures become increased, so are pressures in the pulmonary circulation and the RV workload.*

Consequences of valvular dysfunction on the left side of the heart.

The pressure differences between the left cardiac chambers, LV and LA, are substantial during systole, as are the pressure differences between LV and aorta in diastole. Dysfunction of valves on the left side of the heart may have large consequences for the heart's ability to generate an adequate stroke volume and thus supply the organism with the necessary flow of blood. They also lead to increased pressures in the pulmonary circulation and cause congestion, shortness of breath, pulmonary edema, and reduced oxygenation of the blood.

While stenosis and insufficiency in most patients are separate conditions, the valves of some patients may be both stenotic and insufficient.

The pressure difference between the right-side chambers, and between RV and PA, are much smaller and valvular dysfunction have fewer hemodynamic consequences. All types of severe right-side valve dysfunction may lead to increased venous pressure; isolated RV failure may lead to peripheral edema, ascites, hepatomegaly, etc., while the pressures in the pulmonary vascular bed may be normal or low if LV function remains normal.

Aortic valve stenosis.

This is the most common type of valve lesion in the western world (117); persons born with a bicuspid valve seem to be more at risk for developing such lesions than those with a normal tricuspid valve. The increased workload created by ejection of the SV against a narrowed orifice is similar to the increased workload in severe hypertension; accordingly, most patients have LV hypertrophy, usually of the concentric type (see remodeling above).

In patients with significant narrowing, the peak pressure within the LV is considerably higher than the peak systolic ABP, in severe stenosis, the peak systolic pressure difference may be 40 mmHg or more. The arterial systolic pressure is then not representative of the LV afterload (fig. 3-24). As the afterload of the LV in such patients primarily is determined by the degree of valvular stenosis, the central arterial compliance and the peripheral vascular resistance are of little importance. Vasodilation in patients with a high degree of stenosis does not reduce the LV workload. Instead, a reduction in the diastolic pressure may reduce the coronary perfusion pressure and thus reduce the LV work capacity due to reduced myocardial perfusion. When a progressive increase in stenosis leads to LV failure, diastolic dysfunction also increases, and the diastolic pressure within the LA must *increase* to maintain the preload. Pressures within the pulmonary circulation must be higher than those in the LA to propel the blood forwards; the capillary pressures necessary to maintain a sufficient end-diastolic LV volume may lead to pulmonary congestion and -edema. Common symptoms when heart failure develops are angina (35%), syncope (15%), and dyspnea/heart failure on exertion (50%).

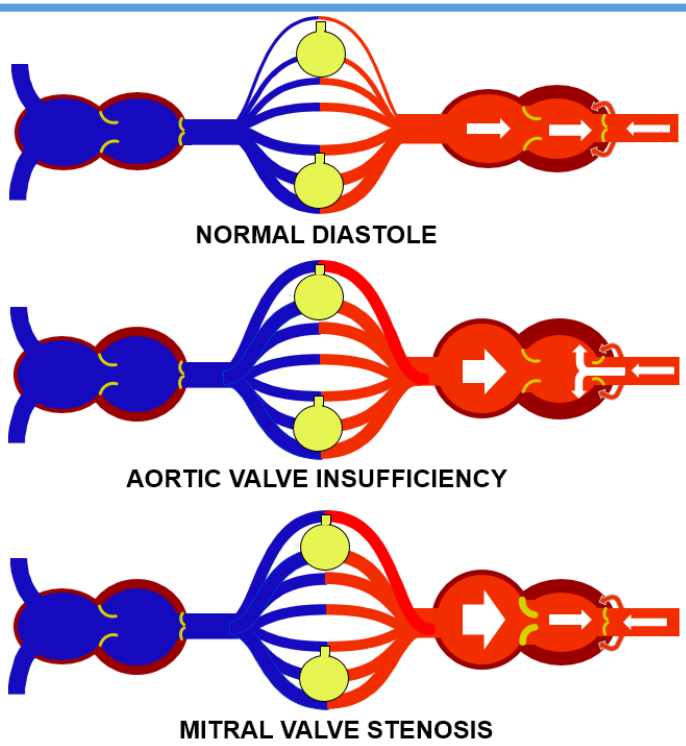

Figure 3-25. *Effects of aortic valve insufficiency and mitral valve stenosis on the diastolic function of the heart. The size of the arrows indicate changes in LVEDP and LVEDV. As LA pressures are increased, so are pressures in the pulmonary circulation and the RV workload.*

Aortic valve insufficiency.

If the aortic valve fails to close properly at the end of systole, part of the stroke volume returns to the LV during diastole (fig 3-25). As the diastolic ABP is much higher than the *normal* LV diastolic filling pressure,

the latter increases even if the myocardium *per se* functions normally during the initial phase. The LA pressures also increase, with similar consequences for the lungs as described above. The constant dilatation of the LV leads to myocardial hypertrophy, most commonly of the eccentric type (see above). Acute severe insufficiency (e.g. endocarditis, dissection of the ascending aorta) in an "unprepared" heart may put an enormous strain on the myocardium and lead to acute cardiac failure, commonly accompanied by pulmonary congestion and shortness of breath.

For both stenosis and insufficiency of the aortic valve, severe dysfunction may involve low diastolic ABP, which again may lead to reduced coronary pressures and myocardial ischemia.

Mitral valve stenosis.

As the leading cause of this defect is rheumatic fever, mitral stenosis has become less common in industrialized western countries. To overcome the stenosis and secure an acceptable LV preload, pressures in the LA and the pulmonary vascular bed must increase (fig. 3-25). In significant stenosis, the preload nevertheless decreases, resulting in reduced stroke volumes and reduced C.O.

The chronic increase in pulmonary vascular pressures leads to changes in lymphatics and the structure of the microcirculatory vessels, including capillaries. These changes protect against the formation of pulmonary edema, many such patients tolerate pulmonary vascular pressures of a magnitude that would precipitate frank edema in non-adapted lungs (118). Common symptoms are fatigue, angina pectoris, and near syncope.

Mitral valve insufficiency.

If the mitral valve fails to close properly during systole, part of the left ventricular SV regurgitates into the LA; the regurgitated volume creates a pressure wave that dilates the LA and continues backwards through the pulmonary circulation and into the PA (fig 3-24). To eject an adequate volume into the aorta, the total LV ejection volumes must increase, requiring an increased LVEDV. The augmented workload of the left ventricle also leads to hypertrophy of the LV wall. Insufficiency may be caused by lesions of the valve apparatus *per se*, but also by dilatation of the LV (functional insufficiency). Dilatation of the LV may stretch the tissue representing the ring (annulus) where the leaflets are anchored to the chamber wall, and prevent them from closing fully (118). Common symptoms of this condition are breathlessness and fatigue.

Acute insufficiency may be caused by rupture of papillary muscle after myocardial infarction, rupture of chordae tendinea caused by degenerative disease, or destruction of leaflet integrity during endocarditis. Such occurrences may result in cardiogenic shock with pulmonary edema (119).

Consequences of valvular dysfunction on the right side of the heart.

Pulmonary valve stenosis.

The main effect is an increased RV workload, resulting in dilatation of the RV and promoting hypertrophy of the chamber wall. If the RV ultimately fails, the RA and venous pressures increase, giving rise to the classical symptoms of systemic venous congestion (see above). A dilated RV may also reduce the LV preload through the mechanism of ventricular interdependence (fig. 3-14).

Pulmonary valve insufficiency.

Analogous to insufficiency of the aortic valve, part of the RV stroke volume returns to the RV during diastole. As the pressure differences between PA and RV in diastole are much smaller than between the aorta and LV, the magnitude of this effect on the RV is less important than that of aortic valve insufficiency on the LV.

Tricuspid valve stenosis

This is a relatively rare condition; the consequence is that the RA must maintain a higher pressure to fill the RV during diastole. If this leads to high venous pressures, symptoms may be analogous to those described for RV failure above.

Tricuspid valve insufficiency

Anatomic dysfunction is rare; in RV failure, however, functional insufficiency is not uncommon. The consequences for LV function are modest, but venous pressures will increase.

Septum defects and rupture of chamber walls (see fig. 3-26 for schematic effects of septum defects on arterial oxygenation).

Atrial septal defects (ASD). Small septum defects on the atrial level, resulting from incomplete closure of the foramen ovale, are quite common and have been estimated to exist in 25-30% of the adult population (120). The aperture of most such defects is narrow; they are seldom a cause of disease and have little impact on the LV diastolic filling volumes. As the mean LA pressures normally are slightly higher than in the RA (about 8 mmHg vs 4 mmHg (26)), there may be a modest and asymptomatic left-to-right leakage of blood. If the RA filling pressures become higher than those in the LA, a right-to-left shunt may be established, creating hypoxemia (fig 3-26, see also Part 4-2).

Escalation of the RA pressure may be a result of increased PA pressure, whether chronic (e.g. chronic pulmonary hypertension), subacute (e.g. severe ARDS), or acute (e.g. pulmonary emboli, venous air emboli during scuba diving). In addition to passage of venous blood, air bubbles and microembolism may also follow the bloodstream and pass directly from the right to the left side of the heart and into the systemic circulation. Such material can, in the worst case, lodge in the brain (121). A minor right-to-left leakage may exist in asymptomatic persons at rest (122); allowing unexpected passage of embolic material from the venous to the arterial circulation.

Congenital ASDs (i.e. septum defects *not* related to the foramen ovale) are much rarer, the consequences are as described above. If the defects are large, a right-to-left shunt may reach a magnitude where the arterial O_2 content is substantially reduced despite normal lung function. An overview of such defects is given in ref. (123).

Ventricular septal defects (VSD). Such defects may be **congenital** (62) and are the most common defect found in children; as about 90% of these close before the age of ten, it is less common in adults. The systolic pressure difference between LV and RV ensures that the direction of the flow represents a left-to-right shunt, with no consequences for the O_2 content of the arterial blood. As the LV ejects part of its stroke volume into the RV during systole, the volume that must be pumped into the PA increases (venous return + volume leaked from LV). As long as the lungs *per se* maintain normal function, such left-to-right shunts do not affect arterial oxygenation. If the RV systolic pressures surpass those of the LV (as can be seen during extremely high PVR), a right-to-left shunt with arterial hypoxemia may be established (see above).

Acute ventricular septum defects may arise suddenly after myocardial infarctions that involve the ventricular septum – typically within 1-5 days after the infarction when the myocardial tissue is necrotic and before the fibrous repair has resulted in solid scar tissue (124). A large-size acute rupture may lead to cardiogenic shock within minutes (see cardiogenic shock below); this is a life-threatening emergency and requires rapid therapeutic interventions.

Rupture of/Injury to the outer chamber walls.

Spontaneous rupture of the outer walls of the cardiac chambers is a rare complication of myocardial infarction (see cardiogenic shock). Traumatic injuries of the outer walls caused by sharp objects (e.g. knives, swords, screwdrivers) or bullets may cause the same type of circulatory catastrophe; as an external thoracic wound can be observed, diagnosis is easier.

Open ductus arteriosus.

The **ductus arteriosus** represents the vascular communication between the aorta and the pulmonary artery during the fetal phase of life, and normally close soon after birth. If it remains open, part of the LV stroke volume flows from the aorta into the pulmonary circulation, creating a left-to-right shunt. Small shunts are usually of no hemodynamic significance, larger shunts may result in LV hypertrophy; the effects on LV, RV, and O_2 in the arterial blood are analogous to that of chronic LV septum defects. If pulmonary hypertension develops, RV hypertrophy ensues. As for septum defects (above), very high pressures in the pulmonary artery may cause a reversal of blood flow direction, creating a right-to-left shunt and arterial hypoxemia.

RIGHT VENTRICULAR FILLING VOLUME AND PRESSURE

Venous return and right ventricular function.

Diminished venous return to the right atrium (e.g. *hypovolemia, venous vasodilation,* and *increased intrathoracic pressure*) reduces the right ventricle end-diastolic volume and it's SV (see above). The pressure-volume curve of the right ventricle is, however, different from that of the left ventricle. During filling with normal volumes, the geometry of the right ventricle changes with little increase in filling pressure, which makes changes in the venous return pressure (measured as central venous pressure, CVP) in the lower range a poor predictor of fluid responsiveness (reviewed. In refs. 125, 126).

Sharp increases in the right ventricle filling pressure (as measured by the CVP) during fluid infusions may, however, be a warning signal that the right ventricle is already di-lated, and that further volume increase may have negative effects on cardiac function (127). Other causes of increased CVP (e.g. pericardial fluid, intrathoracic fluid or air) must, however, be excluded before a final conclusion is drawn.

Right myocardial diastolic dysfunction.

- **Acute overload of an initially normal right ventricle** may be due to high pulmonary artery pressures, pulmonary valve insufficiency, large atrial septal defects, etc. This may induce a ballooning of the right ventricle and diastolic deviation of the ventricular septum into the left ventricle, reducing its end-diastolic volume (*ventricular interdependence*) (54)), see also fig. 3-14. This phenomenon is especially common in patients with positive intrathoracic pressures (e.g. during positive pressure ventilation).
- **Secondary dysfunction with RV hypertrophy** is usually caused by chronic increase in pulmonary artery pressures or congenital malformations.

- **Primary right systolic or diastolic myocardial dysfunction** is often a result of ischemia, cardiomyopathy, etc., see ref. (53) for a comprehensive list of causes of right ventricular failure. Primary failure of the left ventricle may also affect the function of the right ventricle.

Patients with isolated right ventricular diastolic dysfunction may respond negatively to aggressive fluid infusions. If ballooning and/or valvular insufficiency of the right ventricle increases, the C.O. may deteriorate further while the pressure in the central veins (and thus venous pressures in the systemic microcirculation) rises, decreasing the perfusion pressure of the RV myocardium. This type of circulatory failure represents a difficult challenge with limited therapeutic options (see also Part 3-4).

CONGENITAL CARDIAC MALFORMATIONS

Occurrence and general classification

The incidence of heart disease due to congenital malformations in adults in the industrialized world has increased considerably during the last five decades, as the diagnosis and treatment of children with such diseases have made great progress. Some malformations are not seen in adult patients, as they are not compatible with survival to adulthood. The incidence of congenital heart disease reported in the literature varies widely; the majority of centers report an occurrence between 3 and 10 of 1000 live births (128). The prevalence of congenital malformations in adults was, in 2016, calculated to be about six per 1 000 persons (129).

Congenital malformations are often classified as

- **Shunt lesions,** i.e. malformations where part of the blood passes directly from the one side of the circulation to the other without going through the lungs. These often occur as a single defect, the *direction of flow through the shunt* determine the consequences for the O_2 content of arterial blood (see fig. 3-26). Common examples of **shunt lesions** are
  - Congenital defects in the atrium- *or* ventricular septum, *and*
  - Incomplete closure of the foramen ovale *or* an open ductus arteriosus.
- **Simple obstructive lesions**, where the afterload of one or both ventricles is increased due to obstruction of outflow (e.g. subvalvular, valvular or supravalvular stenosis) or increased vascular resistance (e.g. coarctation of the aorta, primary pulmonary vascular hypertension). **Coarctation** is a congenital stenosis of the aorta, usually situated just below the left subclavian artery; the systolic pressure in the upper part of the body is then higher than in the lower part. In patients with high-grade stenosis, an extensive network of arterial collateral circulation may develop.
- **Complex malformations**, where the relationship between the ventricles and the aortic/ pulmonary trunk connections is more or less reversed, and large septum defects compensate in part for the transposition.

Consequences of shunt lesions for oxygenation of the arterial blood.

Lesions causing a *left-to-right shunt* (see above) do *not* increase the venous admixture to the arterial blood and are called **acyanotic lesions**. The flow of blood into the aorta may be close to normal, while that into the pulmonary artery is increased. A ratio between pulmonary and systemic flow below 1.5 seldom causes symptoms, a higher ratio may lead to RV failure (130).

If the pressures on the right side of the heart are increased relative to the left side (as a result of pulmonary vascular hypertension, pulmonary embolization, etc.), a right-to-left shunt,

representing a **cyanotic lesion**, may be established. The size of the defect then determines the degree of venous admixture in arterial blood (see Part 4-2 for shunt calculations).

Large congenital ventricular septum defects cause increased flow and pressure in the pulmonary vascular bed and lead to pulmonary hypertension and RV hypertrophy. If such changes become severe, and systolic pressures in the RV or PA become higher than those in the LV or aorta, the

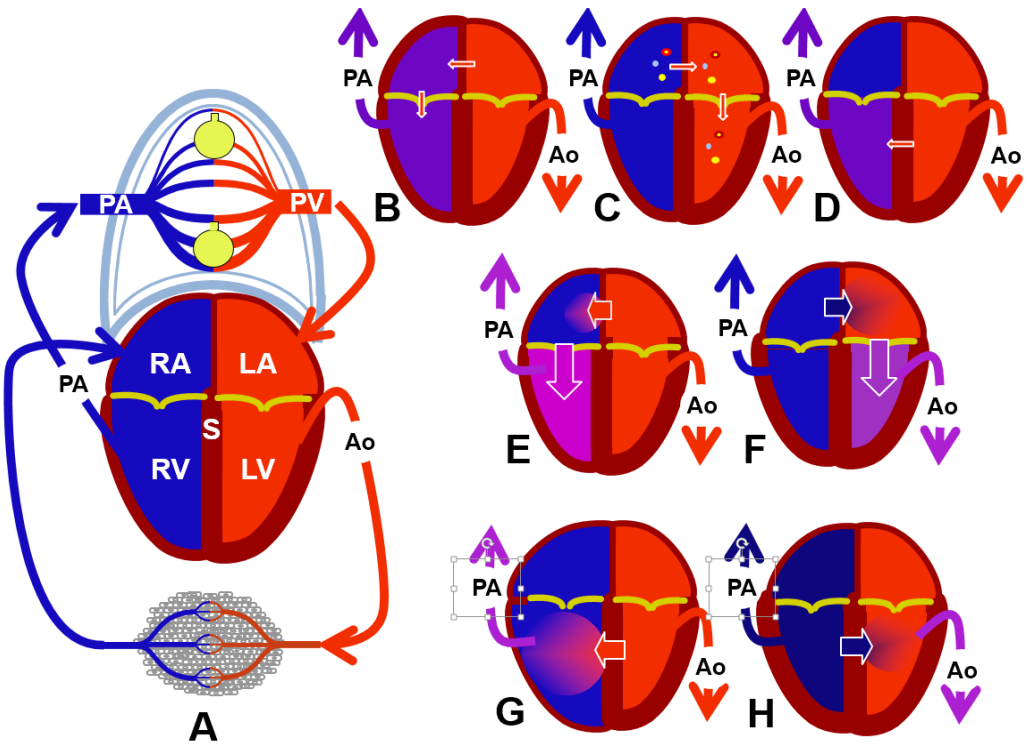

Figure 3-26. *The effect of various types of atrial (A) and ventricular (V) septum de-fects on blood oxygenation in the pulmonary and systemic vascular system, assuming normal lung function.* **A:** *Sche-matic drawing of the chambers of heart (longitudinal axis) and the major vessels.* **RA**: *Right atrium,* **RV:** *Right ventricle,* **LA:** *Left atrium,* **LV:** *Left ventricle,* **S:** *Septum,* **PA:** *Pulmonary artery,* **PV:** *Pulmonary veins,* **Ao:** *Aorta. Colors indicate venous (blue) and arterial (red) O_2 saturation.* **B** *to* **H** *illustrate the consequences of atrial- and ventricular septum defects (ASD and VSD, respectively) on the oxygenation of the blood in the various chambers and in the PA (left. arrow up) and the aorta (A) (right, arrow down).*

B. Small ASD, Left to Right flow. *Aorta, LA and LV: Normal SO_2, in PA, RA and RV: Slight increase in SO_2.*
C. Small ASD, Right to Left flow. *Aorta, LA and LV: Normal to slight decrease in SO_2, in PA, RA and RV: Normal SO_2. Danger of emboli from venous to arterial side.*
D. Small VSD, Left to Right flow. *Aorta, LA, LV and RA: Normal SO_2, in PA and RV: Modestly increased SO_2.*
E. Large ASD, Left to Right flow. *Aorta, LA and LV: Normal SO_2, PA, RA and RV: Substantial increase in SO_2.*
F. Large ASD, Right to Left flow. *Aorta, LA and LV: Substantial decrease in SO_2, PA, RA and RV: Normal SO_2. Danger of emboli from venous to arterial side.*
G. Large VSD, Left to Right flow. *Aorta, LA, LV and RA: Normal SO_2, in PA, and RV: Substantial increase in SO_2.*
H. Large VSD, Right to Left flow (uncommon). *Aorta and LV: Substantial de-crease in SO_2, in LA: Normal SO_2, in PA, RA and RV: Subnormal SO_2 (due to low C_aO_2). Danger of emboli from venous to arterial side.*

direction of the shunt may be reversed also during systole. What was initially an acyanotic state then becomes a cyanotic one. This condition is called the **Eisenmengers syndrome,** characterized by a large **ventricular septum defect** with subsequent **pulmonary vascular hypertension** and **RV hypertrophy**.

In **complex malformations**, there is usually more than one anatomical deviation from normal, and the relationship between the aortic and pulmonary trunks and the ventricles is abnormal. Such malformations are usually **cyanotic lesions**.

In the most common of complex malformation, the **Tetralogy of Fallot**, there is a large ventricular septum defect, aorta overrides both ventricles and receives both oxygenated and mixed venous blood. In addition, there is obstruction of the outflow tract from the RV and RV hypertrophy. Without treatment, only about 11% of the patients survive to reach 20 years of age. In **Transposition of the great arteries**, the RV ejects its SV into the aorta and the LV into the pulmonary artery. Survival is possible only if the venous and oxygenated blood is mixed by passage of blood through an open ductus arteriosus and foramen ovale, or co-existing atrial- or ventricular septum defects. If untreated, only 10% of patients reach six months of age. **Ebsteins anomaly** consists of an abnormal tricuspid valve that creates an RV dysfunction; 80% of the patients have an open foramen ovale or an atrial septal effect through which a right-to-left blood flow occurs and causes a venous admixture to the arterial blood. For details, and excellent illustrations of congenital heart malformations, see refs (62, 131), also other reviews (115, 132, 133, 134).

NODE- AND/OR CONDUCTION DYSFUNCTION

Sinus tachycardia and bradycardia.

Sinus tachycardia (heart rate > 100 BPM) is the physiologic response to increased O_2 consumption and stress *or* reduced C_aO_2. As the mean SV increase in response to increased $\dot{V}O_2$ in normal hearts is around 30%, increased heart rate (to 150-180 BPM) is the only way of increasing the C.O. substantially. Very fast rhythms are, however, ineffective, as both diastole and systole become too short. The duration of the diastole is reduced more than the systole, which decreases the period of effective myocardial perfusion and increases the risk of myocardial hypoxia.

Sinus bradycardia (heart rate < 60 BPM) is a physiologic response to hypothermia, deep sleep, etc., and is also common in well-trained athletes at rest. As the diastolic pause becomes longer, the LV filling increases as do the stroke volumes. In extreme bradycardia, however, an increased SV cannot compensate for the slow rate, and the C.O. can become dangerously low.

Sinus arrhythmias (i.e. intermittent slower and faster sinus rhythm) is usually a physiologic occurrence and is of little clinical consequence.

Arrhythmias and conduction dysfunction.

Cardiac rhythms other than the normal sinus rhythm reduce the pumping capacity of the heart. In atrial fibrillation and A-V block, the "atrial kick" is often lost, making the diastolic filling less efficient (see above); irregular LV contractions lead to variable stroke volumes. Especially in hearts with a dysfunctional myocardium, such arrhythmias may turn a compensated LV dysfunction into an uncompensated one. Some arrhythmias only reduce the *efficiency* of the heart; others involve pauses in LV contractions, causing periods of cerebral hypoxia with dizziness or

syncope. The most dramatic arrhythmias are ventricular tachycardia and total a-v block; these may become life threatening within seconds to minutes (see below).

Supraventricular tachyarrhythmias originate in the SA node (sinus tachycardia) or other locations in the atria and cause tachycardia (premature beats, atrial flutter, and atrial fibrillation). Supraventricular bradyarrhythmias occur if the SA node fails intermittently, a SA pause for longer periods (sick sinus) or permanently (sinus arrest) may lead to bradycardia. Bradycardia may also occur if the impulse from the atria is delayed in the AV node (partial AV block) or fails to activate it (total AV block, third-degree block). In the latter state, ventricular contractions are evoked by the inherent automaticity of ventricular cardiomyocytes; contractions of atria and ventricle are independent of each other. The normal automaticity of ventricles is considerably slower than in the SA or AV nodes, the LV then usually beats with a regular frequency of 20-40 BPM.

Total AV block may progress to ventricular asystole if the ventricular automaticity fails. Block that involves only part of the bundle of His (bundle blocks) may selectively delay or block the impulses to one of the ventricles, abolishing the synchronization of contraction of the two ventricles.

Supraventricular tachyarrhythmias are in principle benign, in the sense that they seldom lead to acute cardiac failure or cardiac arrest. Recurrent and prolonged episodes, however, may induce structural changes in the heart, they are also associated with formation of atrial thrombi and cerebral embolism. Ventricular arrhythmias, on the other hand, vary from those that have minimal effects on cardiac output and have little prognostic importance to those that may progress to life-threatening arrhythmias (Part 3-3).

3-3. CIRCULATORY FAILURE AND SHOCK

INTRODUCTION.

Acute circulatory failure occurs when dysfunction of the circulatory part of the O_2 supply chain (see fig. 3-1, also fig. 3-27 below) threatens the ability to maintain aerobic metabolism in the tissues. In persons with normal cardiac function, a reduced C_aO_2 can, to a large extent, be compensated for by increasing the C.O.; a reduced tissue blood flow (globally or locally) cannot be compensated for by a supernormal C_aO_2. A reduced C_aO_2 may be a result of

- **Primary failure of LV function,** caused by ***i)*** myocardial dysfunction due to *ischemia-hypoxia* or to effects of *drugs and toxic agents,* ***ii)*** acute malfunction of *valves* and/or the *conduction system*, ***iii)*** rupture or perforation of the *ventricular septum* or the *cardiac wall*. Myocardial ischemia induce both systolic and diastolic dysfunction. In rare instances, extreme increases in afterload (vascular impedance, Part 3-1) may induce myocardial failure.
- **Secondary failure of LV function,** caused by *insufficient diastolic filling* ("low preload failure") due to factors located *upstream to the LV* in the "blood flow chain" (fig 3-1) *or* to increased intrathoracic/airway/pericardial pressures. Hypovolemia, acute vasodilation, RV failure, pulmonary embolization, etc. are common causes of such failure.
- **Any combination of the mechanisms above**. Hypotension due to secondary failure reduces the myocardial perfusion pressure, which in turn may lead to secondary LV dysfunction or failure due to myocardial ischemia-hypoxia. In septic shock, both venous return and myocardial function are affected (see below). In addition, primary or secondary failure of *either* left or the right ventricle (RV) function may induce failure also of the other ventricle.

A low ABP may have obvious causes or may even be an intended therapeutic intervention. If unexplained, it should be considered a sign of danger, requiring rapid determination of its cause; early appropriate interventions may prevent a state of cardiovascular dysfunction from progressing to circulatory shock.

Circulatory shock represents a *failure* to maintain a C.O. compatible with aerobic metabolism in the resting organism *despite* a normal C_aO_2 and optimization of LV diastolic filling volume. The term shock is, however, also used to describe states where neither reduced DO_2, nor severe hypotension, may be present (e.g. spinal shock (135)). Generalized failure of aerobic metabolism secondary to mitochondrial damage is often called "cytotoxic shock". A reduced C.O. is associated with low SVs in most patients with circulatory shock; severe reductions in heart rate *may* progress to cardiogenic shock but only in rare instances (136).

ACUTE CIRCULATORY FAILURE, CIRCULATORY SHOCK

An overview of causes of circulatory shock

In a large variety of disease processes, insufficient blood flow causes widespread tissue hypoxia. Circulatory shock have traditionally been grouped by the etiology (137), another way of grouping is by their effect on cardiac function (138).

Circulatory shock due to primary acute cardiac failure.

Cardiogenic shock is a failure of the left ventricle to supply the organism with a flow of blood compatible with normal aerobic metabolism at rest, despite optimization of the preload. In a minority of cases (see below), acute RV failure may prevent such optimization. In most instances, cardiac shock involve LV dysfunction, and can be classified as **systolic**-, **diastolic**-, **valvular**- or

conduction dysfunction, or **any combination** of those. The LV filling pressures and -volumes are usually increased; the pressure increase is transmitted backwards into the pulmonary vascular bed and may lead to interstitial and alveolar edema (fig. 3-27). The RV, which must eject its stroke volume against increased PA pressures, may initially cope with the increased afterload *without* a signifi-cant increase in the venous pressures. After some hours, the RV eventually also fails and the central venous pressures increase.

Circulatory shock with an initially normal left ventricular function.

If we follow the factors involved in the central blood flow (fig. 3-1, 3-27), acute circulatory failure may occur despite a normal LV function and be due to

- **Insufficient venous return, resulting in RV preload failure** (see below), *or*
- **Primary RV failure,** where a failing RV cannot supply the LV with an adequate filling volume despite optimal venous return (e.g. isolated RV failure due to *ischemia/valvular disease*, *primary pulmonary hypertension*), *or*
- **Obstruction of the blood flow between RV and LV** (internal *occlusion, e.g.* pulmonary embolization or external *compression of vessels or chambers, e.g.* positive pressure pneumothorax) or both, or *mitral stenosis.*

Insufficient venous return may be caused by

- **Hypovolemia,** where an uncompensated reduction of blood volume leads to reduced RV filling pressures and –volumes. Decreased RV stroke volumes result in reduced LV diastolic filling and low LV stroke volumes. If the resulting C.O. becomes too low to maintain a DO_2 compatible with aerobic metabolism, the patient is in **Hypovolemic shock.** In such states, the **SVR** is usually high (typically 50% or more above normal) due to massive sympathetic discharge and vasoconstriction. Reduced RV filling may also be a result of external compression of central veins or the chambers of the right side of the heart (see Obstructive shock below) – the consequences for LV preload, and thus the C.O., are the same as in hypovolemia.
- **Distributive shock,** where venous vasodilation causes a discrepancy between the actual volume of blood within the vascular bed and the capacity of the venous vascular compartment. *The consequences for RV and LV diastolic filling are the same as those for hypovolemia; the coronary perfusion pressure, however, may be substantially lower.* As the systemic arteries are also dilated, **SVR may be low,** compounding the effect of a reduced SV on the ABP (Part 3-1). Vasodilation and hypovolemia may co-exist, especially in states with systemic inflammatory changes (see also Septic and Anaphylactic shock).

In Obstructive shock, insufficient filling of the LV despite adequate venous return may be caused obstruction of blood flow due to intravascular (e.g. emboli, fig 3-27), intracardiac, or extracardiac factors. External compression exerted by air, liquid, or tissue pressure in the pleura, mediastinum, or pericardium can reduce the biventricular, or isolated LV, preload despite normal or high filling pressures on the right side of the heart and the pulmonary artery (see fig. 3-27).

Common to the three types of shock types above, except for some variants of septic shock, is that the **circulatory failure is due to insufficient LV diastolic filling volumes.**

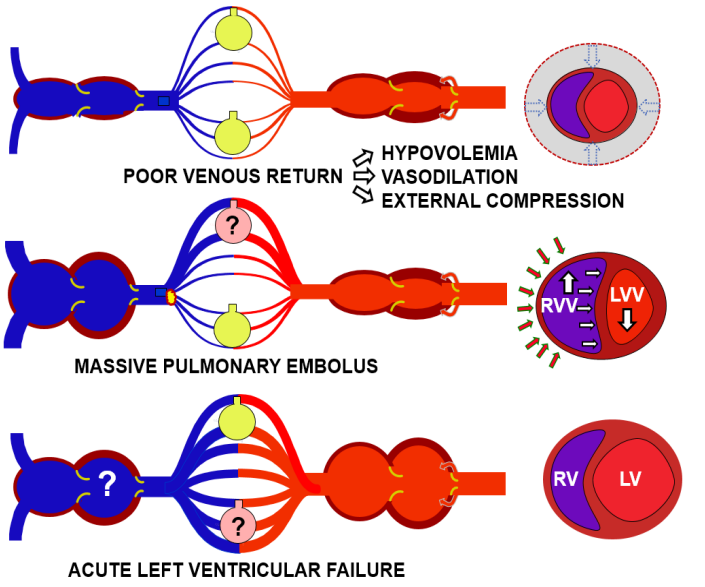

Figure 3-27. *Causes of acute circulatory failure.* **Upper:** *Central circulation during low venous return, preload of both RV and LV reduced.* **Middle:** *Major obstruction of the PA, RV may be dilated and with high diastolic pressures while LV has low pressures. Septum may deviate into the LV, reducing the diastolic preload.* **Lower:** *Primary failure and dilatation of the LV. During the initial phase, the RV may cope with the increased PA pressures (normal CVP); but ultimately the RV also fails and the CVP increases.*

Septic shock is usually classified as a type of distributive shock (139). It differs, however, from the other types of circulatory shock in that the *primary pathophysiological insult* to the organism is not caused by tissue hypoxia, but by the combined effects of toxins and other factors released by invading microorganisms, *and* an excess of pro-inflammatory agents produced by the response of the immune system.

If the cardiovascular consequences of a serious infection progress to shock, the combined negative effects on cardiac function, vascular tone, and fluid loss from the microcirculation (see below) may reduce the DO_2 and lead to tissue hypoxia as a *secondary* event. The period from the triggering event to the development of circulatory shock is usually also different from the other types of shock. It should be considered as a separate entity, different from other types of distributive shock (see below); clinical experience and scientific conclusions based on investigations of patients in septic shock may not be valid for other types of shock.

PATHOPHYSIOLOGY OF THE VARIOUS TYPES OF SHOCK

HYPOVOLEMIC SHOCK.

The state of uncompensated loss of fluid from the intravascular compartment may be caused by either *hemorrhage*, *dehydration*, or *internal loss of plasma fluid.*

Acute hemorrhage.

Acute, major hemorrhage (e.g. traumatic laceration of major vessels, rupture of aortic aneurysms into the abdominal cavity) may result in the development of shock within a few minutes. As the remaining intravascular volume contains all elements of the blood, the Hb may be close to normal during the initial phase before any infusion of fluid has be given. Resorption of interstitial fluid during hypovolemia is a slow process (approx. 500 ml over 15-30 min (140)) and cannot replenish the blood volume fast enough to maintain a normal diastolic filling during major hemorrhage. The intense sympathetic stimulation, however, may mobilize up to 800 ml of blood from the splanchnic circulation within seconds (141).

In other types of bleeding (e.g. gastrointestinal bleeding, bleeding from fractured bone), the loss of blood volume is slower. The circulation may be affected within an hour, but there will be some resorption of interstitial fluid into the circulation and it usually takes several hours for a shock

state to develop. The Hb will be reduced due to dilution by the interstitial fluid, and further reduced when the remaining blood is diluted by infusions of fluid.

The reflexes elicited from the baroreceptors in response to a fall in ABP cause vasoconstriction. This diminishes the decrease in ABP and masks the decrease in C.O. A loss of less than 20% blood volume cause only a modest reduction in ABP; the removal of 1000 ml of blood from anesthetized patients cause a reduction in MAP of only around 8%, the MAP difference between removing 500 ml and 1000 ml was negligible (142). In awake volunteers, removal of approx. 25% of the blood volume reduced the systolic ABP by about 15% (143). The consequences of moderate blood loss vary considerably, however, between published investigations (144, 145). When hypovolemia was simulated by applying incremental sub-atmospheric pressures to the lower body, a C.O. reduction to about 60% of baseline was accompanied by a stroke volume reduction to about 35% of normal; the heart rate increased by 155% but the systolic ABP was well maintained (about 8% reduction) due to an about 60% increase in SVR (146). The ability to maintain a close to normal ABP in the investigations cited above depends on the subjects resting in a supine position, tilting volunteers from supine to a head-up position induces an approximately 25% acute reduction in C.O. even in normovolemic persons (147).

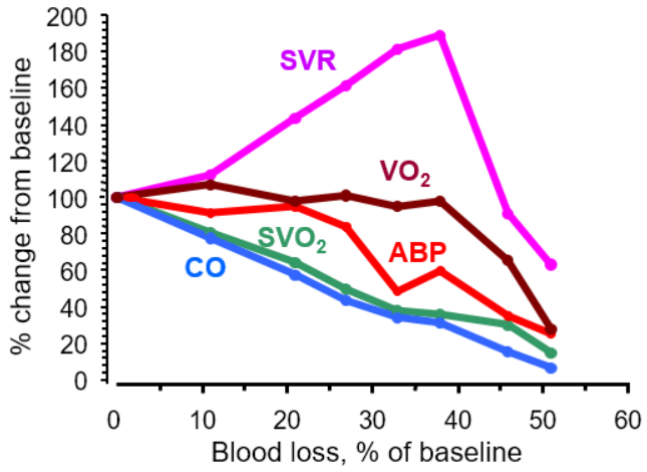

Figure 3-28. *Effects of blood loss on cardiac output* (**C.O.**)*, mean arterial pressure* **(ABP)***, and systemic vascular resistance* **(SVR)***. The effects on mixed venous O_2 content* **(S_vO_2)** *and O_2 consumption* **(VO_2)** *are also shown. All data are given as the percentage of the change from baseline, as calculated from data observed in animal experiments (ref. 74).*

In animal experiments with more severe blood loss, a 20% to 30% reduction in blood volume lowers the C.O. in anesthetized dogs by about 30% to 50%, respectively, while the reduction in MAP with a 30% blood loss is only about 16% (74), see fig. 3-28. In conscious sheep bled for about 30% of their blood volume, the MAP reduction was modest until almost the end of the procedure (148). There was, however, a large variation in tolerance to bleeding between individual animals.

From these and similar data, it may be concluded that *20-30% of the blood volume* may be lost before ABP is significantly reduced. *The* **C.O.**, however, starts to fall within a *blood volume reduction in the 10% range.* In animal experiments, the reduction in SV following loss of blood volume is close to linear within the 0-30% range (fig. 3-28). The percentage reduction in SV is about twice that of blood volume loss; comparable observations have been reported in humans (149). The Committee on Trauma has published a classification of hemorrhage, in which bleeding up to 15% is expected to have little effect on ABP, while a 15-30% blood loss is expected to result in decreased blood pressure (150). Maintaining a close to normal perfusion pressure in the central arteries does not guarantee adequate tissue perfusion when the vascular resistance increases (see above).

In trauma with uncontrolled bleeding, efforts to normalize blood pressures through increasing cardiac preload by infusing large quantities of crystalloids may lead to increased bleeding, due

to a combination of *increased flow* in damaged vessels *washing away clots* and *dilution of the coagulation factors*. To avoid this, but preserve perfusion pressure to vital organs, *permissive hypotension* (with systolic ABP around 80 mmHg) is often advocated until bleeding can be controlled (151). With this level of pressure, a patient with maximal vasoconstriction may still have an inadequate C.O. and remain in a state of shock.

Loss of blood volume due to increased capillary leakage.

In diseases characterized by generalized inflammation and increased microvascular permeability (e.g. sepsis, anaphylactic shock), increased amounts of plasma water and proteins leak from the circulating blood into the interstitial fluid space. In severe anaphylactic reactions, it may become visible as mucous membrane and cutaneous edema within minutes. In sepsis, this process results in the formation of visible edema within hours to days. The fluid volume is lost from the circulation, but not from the organism *per se*, and will re-enter the circulation when normal permeability conditions in the microcirculation are re-established.

Severe dehydration

Severe dehydration that reduces the circulating blood volume to the extent that circulatory shock ensues usually develops over many hours to days. It results from either reduced (or no) fluid intake over several days (e.g. inability to drink, lack of access to water), excessive fluid losses (e.g. increased extravasation of plasma water in sepsis or major burns, excessive sweating in hot climates, profuse diarrhea) or a combination of both. The loss of blood volume (and body fluid volume in general) is mainly loss of water and various electrolytes; the blood concentration of Hb, plasma protein, and electrolytes of such patients is usually substantially higher than normal. If the dehydration is due to profuse diarrhea, electrolyte disturbances may be a more prominent part of the problem than hypovolemia *per se*. The increased blood viscosity (152) may further aggravate the effects of low perfusion pressures and further compromise the flow through the microcirculation.

DISTRIBUTIVE SHOCK

Acute dilatation of the vascular bed: General aspects

When acute vasodilation occurs in a person with normal blood volume (e.g. high spinal injuries or nerve blocks, vasodilating drugs, or toxins), the discrepancy between the intravascular blood volume and the capacity of the vascular bed leads to insufficient venous return to the RV. This reduction of the LV diastolic filling volume is analogous to that during hypovolemia and results in low SV and reduced C.O. In severe cases, this may result in a state of shock, similar to that described for hypovolemic shock above, *except* that the arterial vasoconstrictive element may be missing. The low systemic resistance aggravates the effect of low stroke volumes on the hypotension.

In patients with a reduced systolic reserve capacity, arterial vasodilation may reduce the afterload and facilitate a more efficient systolic emptying of the heart (Part 3-4, Therapy). On the other hand, it may also reduce the myocardial perfusion pressure. As the LV cannot pump more than it receives, a reduction in afterload cannot compensate for a substantial reduction of the end-diastolic filling volume.

In inflammatory states (e.g. anaphylactic reactions, serious infections, post-traumatic and -hypoxic inflammation), increased microcirculatory permeability ("capillary leak") often accompanies the

dilation. The resulting hypovolemia further aggravates the reduction in venous return. Acute vasodilation is especially serious in patients who already have a reduced blood volume due to vasoconstriction (e.g. chronic heart failure, pheochromocytoma) or high tissue pressure (crush syndrome).

During acute vasodilation, the Hb will remain relatively unchanged during the first minutes; if capillary leak occurs simultaneously, the Hb may increase substantially. If oxygenation of the arterial blood is preserved, the C_aO_2 of the blood perfusing the myocardium remains essentially unchanged or increased until the administration of i.v. fluids.

Over time, low capillary pressures will favor resorption of interstitial fluid, gradually increasing the blood volume. This is a slow process (see above), and cannot be expected to compensate for the effects of acute vasodilation on cardiac function in the acute phase.

Vasodilation with normal blood volume.

An otherwise healthy circulation tolerates reductions in perfusion pressure down to a MAP of 50-55 mmHg without detectable organ hypoxia, as long as the C.O. is maintained in the normal or supernormal range (see Hypotension in the vasodilated patient). Pathological vasodilatation may be due to

- **Loss of the normal activity of the sympathetic nervous system** over large vascular areas following high spinal cord or central nervous system (CNS) damage, or central nerve blockade (high spinal or epidural blockades).
- **Vasodilating substances circulating in the bloodstream, or acting locally in the vessel wall.** This may be caused by high concentrations of exogenous or endogenous vasodilators (e.g. NO in gram-negative sepsis, serious liver failure, anaphylactic reactions, post-traumatic and postoperative inflammatory conditions, administration of vasodilator drugs in unintended high doses).

Acute vasodilation increases the capacity of the whole vascular bed. A normal blood volume then results in very low venous return and RV filling pressures. If the filling pressures are not restored by rapid fluid administration and thus increasing the blood volume, *or* the venous return increased by infusions/injections of vasoconstricting agents, the output of the heart declines in the same way as in hypovolemia. Untreated, acute vasodilation may - in addition to low blood pressure caused by low arterial resistance - result in a compromised cardiac output, causing grave hypoperfusion and shock (see below).

In septic shock, usually when caused by gram-negative bacteria, the systemic vascular resistance may be extremely low; values as low as 25% of the normal despite vasopressor treatment can be seen. Even if the heart responds to fluids and inotropes by tripling the C.O., the blood pressure will still be subnormal. The change in MAP can be calculated as a fractional change of each term as a fraction of normal values (**green abbreviations**), using the simplified equation

Actual **MAP** = [**C.O.** x **3**] x [**SVR** x **0.25**]= **MAP** x **0.75** (see also Part 3-1).

Under such circumstances, falling blood pressure will activate the sympathetic nervous system, causing adrenaline and noradrenaline to be released. This in turn will increase both the contractility of the heart (primarily through its effect on $beta_1$-adrenergic receptors) and the systemic vascular resistance (stimulation of $alpha_1$-adrenergic receptors in the vessel walls produces general vascular contraction). These effects, however, are often attenuated in sepsis.

The main danger of low ABP is inadequate perfusion pressures, and thus hypoxic tissue damage, in organs at increased risk; the presence of tissue edema or vascular stenosis exacerbates this risk. As pathological vasodilation occurs on both the arterial and venous side, both fluid infusions (to increase blood volume and venous return) and vasopressors (to mobilize volume by reducing the compliance of the vascular bed) are usually needed to maintain, or re-establish, a normal venous return and thus the RV preload. In addition, the effect of vasopressors on the arterial vessels may also be necessary to establish an acceptable perfusion pressure (see above). The goal should not, however, be to obtain normal arterial pressures, but be tailored to known or assumed perfusion problems of each individual.

Positive pressure ventilation, a therapeutic intervention often necessary in severely ill patients, aggravates the negative effects of hypovolemia on cardiac function but may have positive effects on patients with a dilated heart. These effects are described in more detail below.

Vasodilation with simultaneous loss of blood volume.

The most common etiology of states where vasodilation and increased microvascular permeability reduces venous return is septicemia (mostly conditions involving gram-negative bacteria, see below); a similar version of this circulatory state may be seen after episodes of generalized hypoxemia and/or major trauma, which both create an inflammatory response (153, 154, 155, 156). In most septic patients, the process evolves gradually over hours to days; in certain types of acute immunological reactions like anaphylactic shock, hyperacute loss of blood volume (capillary leak) combined with massive vasodilation may lead to circulatory collapse and very low (or undetectable) ABP within minutes. In extreme cases, the estimated loss of the plasma volume to the interstitial space may amount to up to 35% of the previous blood volume during the first 10 minutes (157).

SEPTIC SHOCK: not only dysfunctional blood distribution.

Septic shock is a condition where an uncontrolled inflammatory reaction to invading microorganisms elicits a combination of ***i)*** *vasodilation*, ***ii)*** *compromised cardiac function, iii) reduced perfusion pressures* and ***iv)*** *microcirculatory dysfunction*. In addition, agents released by microorganisms and the inflammatory response may change the *metabolic function of the cells* (see below). When pronounced, the sum of such changes leads to failure of *both* O_2 tissue delivery *and* utilization, i.e. a state of septic shock.

Septic shock is usually classified as "distributive shock" (158); one theory is that the O_2 supply to the organs may be adequate but that perfusion is maldistributed within the tissues (159, 160). Another theory is that the ability of the cells to utilize the delivered O_2 is reduced by mediators released by either the microorganisms themselves, endogenous cells exposed to proinflammatory stimuli, or both (161). In the following, the focus will be on the failure of the *macrocirculation*, as this is easiest to investigate and where treatment is relatively standardized.

Sepsis and the heart.

In addition to causing vasodilation, bacterial toxins have a **negative effect on cardiac contractility**, as do other substances that are produced by the body's cells under the influence of such toxins (e.g. nitrogen monoxide (NO), cytokines). This may partly be compensated by the increase in cardiac compliance often found in such patients, increasing the end-diastolic volume at normal filling pressure (reviewed in ref. 162). Such dilatation results in a reduced EF (see previously), but may nevertheless be associated with increased survival (163, 164, 165).

The low vascular resistance and reduced afterload make it possible for the C.O. in patients with previously normal hearts to be maintained or even substantially increased (*hyperdynamic circulation* with C.O. up to 2-3 times normal) if the diastolic filling volume is optimized and there are ongoing infusions of catecholamines. In certain conditions (e.g. meningococcal sepsis), the myocardium may be so weakened by bacterial toxins, proinflammatory cytokines, and intravascular coagulation, that the heart fails *despite* an extremely low afterload.

The three phases of septic shock (numbers in the text refer to fig. 3-29).

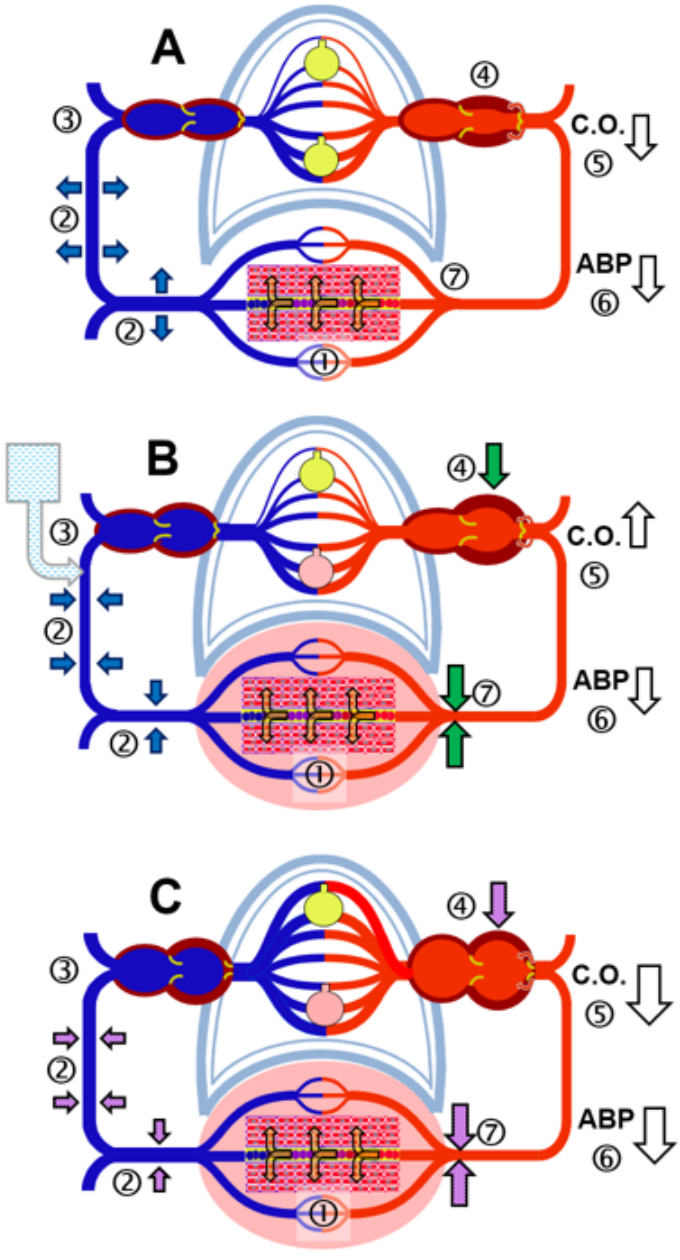

Figure 3-29. *The three phases of serious sepsis and septic shock.* **A:** *Early phase.* **B:** *Compensated phase, responding to therapy.* **C:** *Irreversible septic shock. See text for symbols and details.*

In the initial phase (A), a combination of *fluid loss* from the microcirculation ① and *vasodilation* ② reduce the venous return ③ and thus the LV preload ④. In addition, myocardial contractility declines and the C.O. ⑤ decreases further. ABP ⑥ is low, as the normal vascular response to endogenous and exogenuous catecholamines is impaired and the SVR is reduced ⑦ In the **compensated phase (B)**, fluid loss ① continues but is compensated by fluid infusions, and vasopressors ② mobilize blood from the dilated veins and increase venous return ③. LV preload ④ is secured; with inotropic support of myocardial contractility and a reduced vascular resistance, the C.O. ⑤ increases. ABP usually remains reduced, as infusion of vasopressors ⑦ are less effective than during normal conditions.

The condition may progress to **irreversible** or **refractory septic shock (C),** where the effect of fluids, vasopressors and inotropes are attenuated and cannot reverse the condition. The myocardium fails and the heart dilates; the low C.O. combined with massive dilatation of the systemic vascular bed reduces the ABP to levels where adequate perfusion pressure of the vital organs can no longer be sustained. In this phase, the ability of the cells to utilize the supplied O_2 may also be reduced by metabolic changes induced by the septic process (see above).

OBSTRUCTIVE SHOCK

Obstructive shock is the least common of the shock types. The two main mechanisms precipitating obstructive shock are

- **Obstruction** of the blood flow *through* the central circulation, or *within the heart* itself **by intravascular** or **intracardiac space-occupying entities** (e.g. emboli, thrombi, cancers, implanted- or foreign objects).
- **Obstruction of diastolic ventricular filling by external forces**, i.e. compression of major vessels or the heart itself by any process that increases the intrathoracic or intrapericardial pressure, or in other ways limits the expansion of the cardiac chambers during diastole.

Major pulmonary embolization (PE).

This is the most common cause of obstructive shock; estimates of the incidence of shock caused by PE in larger series have been reported to be 4.2% (166), 9% (167) and, recently, 13.9% (168). Life-threatening embolization has traditionally been associated with embolic occlusion of about 50% or more of the pulmonary vessels. For the individual patient, the underlying circulatory state as well as the reserve capacity of the heart for dealing with the circulatory effects of embolization, determines the consequences (169). In PE patients arriving at the hospital in *circulatory shock*, the combined hemodynamic and hypoxic consequences (Part 4-3) of major embolization may be rapidly lethal; mortality rates of 84% were reported in 1976 (170) vs 76.6% reported recently (168). Among those who die from such shock, the majority previously succumbed within the first hour after the onset of symptoms, leaving only a narrow window of opportunity for diagnosis and therapy (169). Despite increasing sophistication in emergency and ICU diagnosis and treatment available for those who reach the hospital alive, about 40% of the in-hospital deaths after PE still occur on the day of admission.

The typical **changes in central hemodynamics** (see Part 4-3 for blood gas changes) are

- A combination of *mechanical obstruction* of some vessels in the pulmonary circulation and *vasoconstriction* of other, non-occluded vessels due to chemical- and reflex effects may increase pulmonary vascular resistance dramatically. High end-diastolic filling pressures and dilatation of the RV (ballooning) occurs if the RV fails to cope with high pressures in the pulmonary artery (see also Part 4-3, Pulmonary edema). Failure of a previously healthy RV to generate pressures necessary to force the blood through the pulmonary vessels that are still open deprives the LV of the necessary preload; the upper mean PAP that can be generated by a previously normal RV seems to be limited to a pressure of 40 mmHg (171).
- A shift of the ventricular septum towards the left side of the heart (ventricular interdependence (172, 173)). The reduced output of the RV results in reduced filling pressures in the LV, the septum shift is a result of high EDP in the RV and low in the LV. The reduced SV is a consequence of a reduced LVEDV (fig. 3-14).
- Low LV stroke volumes lead to low ABP, while the RV and RA pressures, including the CVP, may increase. The reduced perfusion pressure may render the myocardium of both the LV and RV hypoxic and contribute to the creation of a vicious circle. In addition, the hypoxemia usually associated with a major PE may aggravate the situation further.

Other types of obstructive shock.

The hemodynamic consequences of other types of obstruction depend on their localization. If proximal to the RV, the diastolic filling of both cardiac chambers is impeded. If distal to the RV,

but proximal to the LV, it imposes an RV afterload increase that cannot be compensated for by increases in myocardial contractility. An obstruction at, or beyond, the outflow from the LV, biventricular failure and -dilatation can be expected.

If pressures in the right atrium increase more than those in the left atrium, patients with an open foramen ovale (or other atrium septal abnormalities) may develop a right-to-left shunt; this may aggravate an arterial hypoxemia.

The most common conditions, other than PE, where obstruction impedes LV filling, are

- **Increased intrathoracic pressure** (e.g. positive pressure pneumothorax, major intrathoracic bleeding or effusions, space-occupying processes) may impede end-diastolic filling of both ventricles by reducing the transmural pressure, and thus the effective end-diastolic filling pressure, of the heart.
- **Increased pericardial pressure** (e.g. tamponade due to effusions *or* bleeding, constrictive pericarditis) may inhibit the end-diastolic filling of the heart to an even greater degree. For both of the above conditions, *increased filling pressures* on both sides of the heart are combined with *low filling volumes*; extrapolating from filling pressures to -volumes in such patients may jeopardize the correct choice of treatment.

Positive pressure ventilation also increases the intrathoracic pressure but to a less dramatic degree; the effect is more related to lung expansion, i.e. the intrathoracic volume increase, than to the airway pressures *per se*. On the other hand, the latter may obstruct the microcirculatory flow by increasing the perivascular pressures. In *hypovolemic* patients, hyperinflation of the lungs may cause severe reductions in SV and blood pressure; accidental high airway pressures during mechanical ventilation (Part 4-4) may have similar effects on preload as a positive pressure pneumothorax and cardiac tamponade.

CARDIOGENIC SHOCK.

The most common cause of cardiogenic shock is acute myocardial infarction (**AMI**). The incidence of cardiogenic shock after AMI is around 7-8% (174, 175, 176); when shock develops in patients that reach the hospital alive, the mean time between the start of AMI symptoms to the diagnosis of shock is established is around 6 hours (177).

A multitude of cardiac events is associated with cardiogenic shock (178). Ischemia, which affects both systolic and diastolic function, is the most common etiology of acute myocardial dysfunction (179). In one study, extensive myocardial ischemia was the cause of about 75% of the cardiogenic shocks, followed by acute mitral valve regurgitation (about 8%), ventricular septal rupture (about 4.5%), and primary RV failure (about 3.5%) (180). The absolute percentages vary somewhat between different reports; the relative importance of the various etiologies is, however, largely similar (178, 181, 182, 183).

Other conditions, like acute myocarditis and acute valvular failure due to endocarditis, may also induce cardiogenic shock. Severe dysfunction of the left ventricle may be secondary to septicemia, illegal drugs or legal drug overdose, toxins, intoxications, etc. Of special interest is that some of the newer anticancer and antiviral agents have cardiotoxic effects in some patients, this is probably mediated by their effect on the mitochondria (reviewed in ref. 184). In patients who have suffered cardiac arrest, post-resuscitation, i.e. post hypoxic, vasoplegia may develop (156). This leads to shock characterized by low C.O. *and* very low vascular resistance with a poor response to vasopressors; resembling the circulatory state of late septic shock (see above).

LV failure due to acute myocardial infarction (AMI).

Myocardial ischemia will progress to acute myocardial infarction (AMI) if successful reperfusion interventions (thrombolysis, blocking, and stenting of occluded coronary arteries) cannot be implemented. The 2012 universal definition of AMI includes *all* instances where there is evidence of even minute myocardial necrosis (185). An AMI that involves the full thickness of the left ventricular wall causes an elevation of the EKG ST-segment and is designated STEMI (**ST-E**levation **MI**) while AMIs that do not involve the full thickness do not cause clear-cut elevations and is designated NSTEMI (Non-STEMI). Whether an AMI precipitates circulatory failure or not depends on the size as well as the localization of the infarcted area. If the ischemic (or infarcted) area is large, the left ventricle cannot maintain a C.O. (and thus DO_2) compatible with resting baseline $\dot{V}O_2$ despite optimization of end-diastolic volumes and titrated reduction of the vascular resistance to ejection of the SV. The patient is then in cardiogenic shock.

The mechanical complications that may induce acute cardiogenic shock or sudden death occurring *secondary* to localized ischemic necrosis (acute mitral valve regurgitation, septal- or free wall rupture) usually occur during a period of 2 days to 2 weeks after the infarction (186).

Isolated infarction of the RV may also induce shock if the myocardial injury severely impairs its pumping capacity. Isolated RV dysfunction occurs in about 3.4 % of cardiogenic shock patients (187). Due to small RV stroke volumes, the diastolic filling of the LV becomes insufficient and may result in shock even if the myocardial contractility of the LV *per se* is preserved in the initial phase. Most circulatory changes are similar to those resulting from massive pulmonary embolization (see above); the *PA pressures* will, however, be *normal or low* as the stroke volume of the RV is small and there is no pulmonary vascular obstruction.

The diagnosis of cardiogenic shock depends on the presence of hypotension and manifestation of the classic symptoms and a probable cardiac etiology:

- **Systolic BP (SPB) < 90 mmHg** for > 30 min *or* a need for vasopressors to keep SPB > 90 mmHg.
- **Pulmonary congestion** *or* elevated left ventricular diastolic pressures.
- Signs of **impaired organ perfusion** with *at least one* of the following: *a)* altered mental status, *b)* cold, clammy skin, *c)* oliguria and *d)* increased blood lactate,

plus an educated assumption of cardiac etiology (178).

In normothermic persons, an acute reduction of C.O. by less than 30% (from the lowest normal indexed C.O., CI, of 2.5 l/min/m^2 to 1.8 l/min/m^2) may precipitate a state of shock (188). If the CI fails to increase to 2.2 l/min/m^2 or above after appropriate interventions (including inotropic support and preload optimization and afterload reduction) aiming to optimize cardiac function, a diagnosis of cardiogenic shock also applies (189, 190).

Reversible LV dysfunction in cardiogenic shock.

Stunning (see also above**)** is a reversible dysfunction of myocardial function that may progress to cardiogenic shock; it is usually seen after ischemia-reperfusion states (191), after cardiac surgery (192), and post-resuscitation (193), but *may* also occur in connection with acute emotional stress and high levels of catecholamines (194). In stunning, improvement or normalization of cardiac function is usually seen within 24-48 hours (195) if appropriate therapy prevents further damage to the heart.

Drugs and toxic substances.

An overdose of many legal drugs (e.g. Ca^{++} channel blockers, beta-blockers, tricyclic antidepressive agents, local anesthetics) may cause severe LV failure and death (196), as do several illegal drugs and toxic agents. Patients who survive (some with the help of extracorporeal circulatory support) may regain normal cardiac function (197).

Acute mechanical complications to AMI and endocarditis.

Mitral valve regurgitation. Ischemic damage and rupture of the papillary muscle fibers that close the mitral valve when systole commences impair effective valve closure; such rupture usually occurs 2 to 7 days after an inferior infarction (119). As the pressure opposing ejection into the left atrium is smaller than into the systemic arterial bed, part of the left ventricle SV regurgitates backward into the left atrium (fig. 3-24). If the part ejected into the aorta is insufficient to maintain systemic flow and aerobic metabolism, cardiogenic shock develops. The part of the SV that regurgitates into the left atrium increases the pressures in the pulmonary veins and capillary bed and may cause fulminant pulmonary edema. Myocardial function then suffers from the combined effects of reduced perfusion and hypoxemia.

In endocarditis, acute infectious destruction of the mitral valve, as well as the aortic valve, may precipitate serious heart failure and cardiogenic shock. *Paravalvular* leakage also occurs. The hemodynamic symptoms are, in principle, similar to those of MI following AMI but the contractility of the myocardium may be better in the initial phase.

Rupture of the myocardium.

Rupture of the myocardial septum.

Rupture of the ventricular septum may occur a few days to 2 weeks after myocardial infarction (acute VSD) and causes part of the ejected LV stroke volume to enter the right ventricle. The RV then has to pump an increased blood volume into the pulmonary vascular bed. If the SV ejected into the aorta is insufficient to maintain aerobic metabolism, cardiogenic shock develops. The blood entering the RV through the rupture has already been oxygenated in the lungs; the blood entering the pulmonary artery thus has a higher O_2 content than normal while that of the superior vena cava is reduced due to the systemic circulatory failure. In patients with a PA catheter in place, this type of discrepancy is diagnostic for a ventricle septum defect.

Rupture of chamber walls.

This may be a complication of transmyocardial infarction, approximately 50% occur within the first 1-5 days after infarction but some may arise as late as 2 weeks after. Blood is pumped into the intact pericardial sac with a pressure equal to the systolic ABP and the chambers of the heart rapidly become compressed. As the transcardiac pressures fall, diastolic filling of the ventricles diminishes and the LV stroke volumes become minuscule. Shock may occur within seconds to a few minutes. Traumatic injuries of the outer walls caused intentionally by sharp objects (Part 3-2) may cause the same type of circulatory catastrophe; as the pericardium is also penetrated, rapid exsanguination into the thoracic cavity and severe hypovolemia may be more important than pericardial tamponade for development of shock.

Dysrhythmias, severe bradycardia.

Acute dysrhythmias

Myocardial ischemia may cause arrhythmias and various types of impulse blockade. Arrhythmias *per se* do not usually induce shock; when combined with ischemic systolic and diastolic dysfunction they may, however, aggravate the circulatory failure. In the case of rapid heart action at a rate above 140-150 (especially associated with atrial fibrillation) in patients with cardiomyopathy, the diastolic filling is also reduced (198).

Arrhythmias are commonly seen during the reperfusion phase after a period of ischemia; in addition, infarction of areas encompassing the main conduction pathways can lead to blockage of the electrical signals. The occurrence of ventricular tachycardia after myocardial infarction is associated with an increased risk of ventricular fibrillation (199). This is the ultimate arrhythmia and is lethal unless rapid treatment is instituted (see cardiac arrest below). Acute changes in the conduction system may also lead to cardiac failure. Such changes can occur as a result of hypoxemia (200), electrolyte imbalance (201), drugs (202, 203) and drug overdose (204), serious infections (205) or intoxications (206, 207).

Moderate bradycardia is generally well tolerated. In the aftermath of cardiac arrest, sinus bradycardia at a rate of around 50 bpm is even associated with a better outcome (208). Severe bradyarrhythmias may cause hypoperfusion as well as pulmonary congestion. Many, but not all, patients will respond to atropine, moderate doses of catecholamines with a strong chronotropic effect (e.g. isoprenaline, dobutamine, and adrenaline) increase the heart rate in most patients that do not respond to atropine. In non-responders, emergency cardiac pacing may be an option (209, 210).

CARDIAC ARREST.

A cardiac arrest will ultimately occur in all persons; before the advent of the brain death concept it defined the moment of death (211, 212, 213). In acute medicine, cardiac arrest is usually defined clinically as a *suddenly occurring state of unconsciousness combined with a lack of detectable pulse*, both assumed to have a cardiac etiology, and occurring within the frame of the "Sudden Cardiac Death – SCD" concept (214). Cardiac arrest may also be a planned therapeutic intervention (e.g. induced cardiac arrest during cardiovascular surgery); in such situations, cooling of the organism (Part 2-3), the establishment of a mechanical cardiopulmonary bypass (see below), or a combination of both, prevents hypoxic damage to the brain and the rest of the organism.

Cardiac arrest is the ultimate circulatory failure; all blood flow through the microcirculation ceases when the pressure in the aorta falls to the level of venous pressure, usually within 30-50 seconds (215, 216). After total arrest of the cerebral circulation, consciousness is lost within 4-10 seconds (217). Agonal respiration (gasping) can, however, be observed for minutes after clinical cardiac arrest in humans (218, 219) and is also observed under controlled circumstances in experimental animals (220). Such gasping has been found to be associated with increased survival (219), but may also be misinterpreted as a sign of life by bystanders, and thus delay the start of cardiopulmonary resuscitation (CPR).

In ICU patients where active treatment is withdrawn due to a judgment of futility, mechanical activity of the heart (i.e. the ability to generate a stroke volume detectable as a pulse in the

arterial pressure curve) is terminated several minutes before the cessation of electrical activity detected by EKG in 90% of the patients (221).

Pathophysiological conditions associated with clinical diagnosis of cardiac arrest are,

- **Asystole**, i.e. no dectable spontaneous electrical or mechanical activity of the myocardium.
- **Ventricular fibrillation (VF)**, where disorganized cardiomyocyte contractions fail to generate pulse-giving stroke volumes.
- **Electromechanical dissociation (EMD)**, where there are detectable QRS complexes but no, or very feeble, contractions. The latter are of insufficient force to create a SV large enough to create a palpable pulse, and the C.O. cannot sustain aerobic metabolism (222).

A **very rapid ventricular rhythm** (ventricular tachycardia) may also fail to generate stroke volumes that result in a detectable pulse. Clinically, such patients are often assumed to be in cardiac arrest as they are both unconscious and without a detectable pulse. This type of rhythm often progresses to ventricular fibrillation (223).

The most common cause of cardiac arrest is acute myocardial ischemia, due to either localized coronary ischemia (i.e. myocardial infarction) or secondary to generalized hypoxemia; during the latter, bradycardia usually precedes ventricular fibrillation (224). In addition, electrolyte abnormalities, poisoning, trauma, electrical shock, myocarditis, and a long list of other conditions may cause cardiac arrest (225).

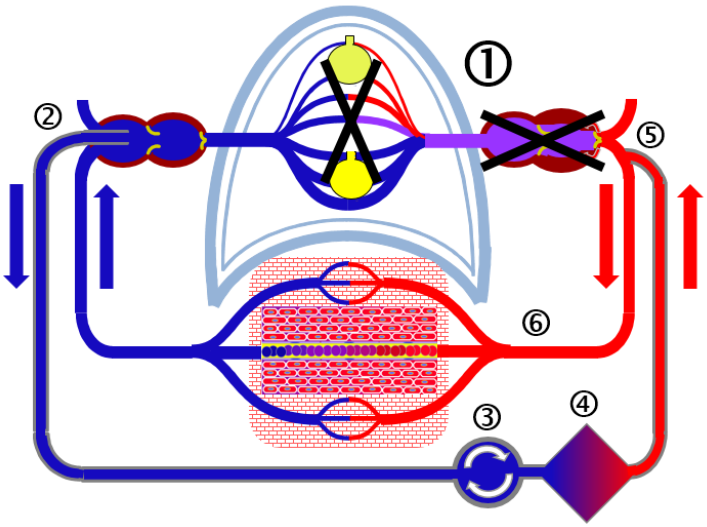

Fig 3-30. *Extracorporeal circulation during cardiac arrest. When there is no pumping activity of the left ventricle ①, all flow to the organism is supplied by an external circuit. The venous return ②is drained by a pump ③, which forces the blood through a membrane oxygenator ④. The fully oxygenated blood enters the upper aorta through a cannula ⑤and follows the normal pathway ⑥to the various organs. The DO_2 is determined by the pump flow and the C_aO_2. The lungs receive no blood flow and do not participate in the gas exchange; CO_2 elimination is regulated by the magnitude of gas flow through the oxygenator.*

Primary treatment focuses on the start of cardiopulmonary resuscitation (CPR) and electro conversion of "shockable rhythms", i.e. ventricular fibrillation and pulseless ventricular tachycardia, as soon as possible. The most advanced CPR with the help of mechanical devices may generate a flow to the brain corresponding to 30-60% of normal, while the coronary flow (which is crucial for regaining cardiac function) is only some 5%-20% of normal (226). Despite this, *early* start of CPR is the most important independent predictive factor for survival (227, 228). The intracardiac or i.v. injection of adrenaline, long considered a mainstay in resuscitation, may increase the primary return of spontaneous circulation (ROSC) (229) but does not appear to increase survival. The benefits of its use in out-of-hospital cardiac arrest is still debated (230, 231).

In selected patients with cardiac arrest refractory to initial treatment (especially when the arrest is associated with hypothermia), establishing extracorporeal life support (fig. 3-30) until underlying etiological factors have been corrected can be lifesaving (232). The resources needed to institute such treatment within a reasonable period are, however, limited and its impact on mortality *in general* is uncertain. Case histories with successful outcome after extracorporeal support, especially in patients with hypothermia, have been published (see Part 2-4).

3-4. ACUTE CIRCULATORY FAILURE AND SHOCK: DIAGNOSIS, THERAPY, AND MONITORING

INTRODUCTION.

Regardless of whether severe circulatory failure is in the early stages*or* has already progressed to a state of shock, correct identification of the cause is a prerequisite for effective therapy. Rapid and appropriate interventions may avert the progression from circulatory dysfunction to failure and shock (see the "Golden Hour" below). The period available for implementing interventions that may prevent such progression varies considerably, however, as to pathophysiological etiology as well as available resources. Information that could prove useful for logical deductions leading to rational therapy may be lacking during the time window where early therapeutic interventions might stave off progression from circulatory instability to shock. Despite this, interventions aiming to maintain or re-establish adequate tissue O_2 supply (see below) must not be delayed if hypoxic damage to the tissues is to be avoided (Part 2-4: Ischemia-Reperfusion).

In out-of-hospital cardiac arrest, information about previous diseases or events leading up to the arrest may not be available. The clinical diagnosis is, however, easy and treatment is fairly standardized. In the initial phase of circulatory shock, the underlying processes are not always obvious; the choice of treatment strategy depends on whether the precipitating cause resides within the heart itself (cardiogenic shock), is caused by LV preload deprivation and/or arterial vasodilatation (e.g. hypovolemia, sepsis) or central circulation (e.g. massive pulmonary embolism).

In some patients, the type of shock may be obvious. Typical examples are hemorrhagic shock in patients with visible major bleeding, cardiogenic shock in patients with acute chest pain and STEMI EKG pattern in most localizations, especially when accompanied by dyspnea (interstitial edema, incipient alveolar edema) or fully developed pulmonary edema. Jugular vein congestion may be an indicator of right cardiac failure which may, or may not, be secondary to left ventricular failure.

In others, establishing the correct diagnosis may be complicated. Elderly cardiac patients with known cardiac disease may have occult gastrointestinal bleeding, while previously healthy young people may suffer from pericarditis, myocarditis, or cardiac tamponade following injury. In rare instances, massive (and potentially lethal) myocardial infarction may be seen in well-trained young athletes with hypertrophied myocardium (233). Persons with an established cardiac dysfunction may respond differently to interventions expected to be beneficial in persons with normal hearts (see Part 3-2 diastolic dysfunction, cardiomyopathies), it is therefore important that also medical personnel without special training in cardiology and circulatory pathophysiology have some basic knowledge of cardiac dysfunction and failure.

Scientific data describing the effects of re-establishing or optimizing O_2 delivery in severely ill patients are difficult to interpret, as harmful biochemical processes leading to organ dysfunction or failure (e.g. "damage-associated molecular patterns - alarmins" (234) "cytokine storm" (235)) may already be in progress when the patients fulfill the inclusion criteria for shock established by the investigators. In addition, accurate hemodynamic measurements, as well as material for laboratory analysis, can be difficult to obtain during the initial, hyperacute phase of circulatory failure. Conclusions based on data obtained from studies of ICU patients, where attempts at circulatory stabilization often are ongoing and cellular dysfunction may already be established, may not be valid for previously healthy patients during the early phase of an emergency.

Basic classification of circulatory failure and shock, relative to therapeutic strategies (see also Therapeutic options).

Of paramount importance for the choice of therapeutic interventions is a rapid determination of whether the circulatory failure *primarily* is caused by

i) LV dysfunction due to insufficient end-diastolic filling volumes (LV "hypovolemia"),
ii) LV dysfunction due to failure of the cardiomyocyte function, *or*
iii) Pathological changes in the structures of the heart (e.g. dysfunction of valves or the impulse conduction system, rupture of the septum or outer walls (see Part 3-2).

The distinction above is of little importance from a tissue O_2 supply viewpoint. In animal experiments, the consequences of reduced DO_2 for the tissues seem to be similar whether the hypoxia is due to anemia, hypoxemia, or low flow (236, 237). Correct diagnosis is, however, of crucial importance for the choice of therapeutic strategies. Diagnostic, and subsequent therapeutic, errors (e.g. massive fluid infusions in cardiogenic shock, vasopressor therapy in severe hypovolemia) can lead to alveolar or tissue edema and aggravation of the tissue oxygenation failure, respectively.

Some of the clinical signs and changes in hemodynamic parameters associated with circulatory failure are non-specific (i.e. common to most shock states, regardless of etiology); others may help to discriminate between various etiologies. Expected changes in various parameters, as well as their precision, are outlined below. The examples presented are based on the assumption that there is only *one* etiology present; in real life, more than one factor may contribute to the circulatory failure. Common examples are ***i)*** hemorrhage (hypovolemia) and positive pressure pneumothorax (obstruction of venous return) in trauma victims, ***ii)*** capillary leak (hypovolemia) and myocardial dysfunction (systolic heart failure) in sepsis, and ***iii)*** pulmonary embolization (obstruction) and myocardial dysfunction in patients with chronic heart failure. In addition, both overdoses of prescription- and illegal drugs, as well as various toxins, may complicate the picture, as can various congenital diseases.

A logical choice of intervention(s) depends on understanding the underlying pathophysiology; such understanding also helps in making an educated assumption about possible etiologies (Part 3-2). An erroneous interventional strategy not only fails to offer the possibility of stabilization or recovery but may be harmful and potentiate a vicious negative circle (see above).

The Golden Hour concept in circulatory failure.

The Golden Hour concept has its origins in the First World War, where an association between the time elapsed before initiation of appropriate therapy and subsequent mortality in a limited number of wounded soldiers was reported (238, 239); similar results for combat casualties in Afghanistan have recently been published (240). The validity of this concept in civilian trauma has, however, been questioned by some authors (241, 242). A time span of exactly one hour is a simplification and lacks adequate documentation. On the other hand, the principle of avoiding shock by rapid therapeutic interventions and terminating any shock state as quickly as possible is pathophysiologically sound and may reduce the risk of hypoxic mitochondrial damage. This principle is also reflected by the fact that the Surviving Sepsis Campaign recently changed its recommendation for the time frame for infusion of the first 30 ml/kg of crystalloid fluid in hypotensive or lactacidotic patients from three hours to one hour (243).

Inadequate DO_2 with generalized hypoxia results in a generalized, inappropriate inflammatory response in the form of a "cytokine storm" (155); the length of the period between start of tissue ischemia and reperfusion is crucial for the ability of the tissues to regain normal function (98). Appropriate interventions that can be initiated within the shortest possible time are therefore of great importance for the outcome of the shock patient; in some situations, such interventions must be initiated *before* the etiology of the shock state has been clarified.

A combination of increased F_iO_2, fluid infusions and injections/infusions of vasopressors and/or inotropes are usually employed to keep the shock patient alive until a diagnosis is made and appropriate therapy instituted. The emphasis on the possible negative aspects of such modalities in some parts of scientific literature (244, 245, 246, 247) should not lead to fears of employing such interventions before the final diagnosis is established; the possible hazards of any intervention must always be weighed against the alternative of *not* intervening.

Once the diagnosis has been clarified, the need for continued infusions of fluids/blood products and the use of vasopressors/inotropes should be re-evaluated. Interventions aimed directly at the triggering event (e.g. surgical and/or radiological interventions for hemorrhage or myocardial ischemia, thrombolysis or removal of acute pulmonary emboli) may have a higher priority than continuing efforts to achieve here-and-now circulatory stabilization. Other appropriate interventions may consist of therapeutic *drugs* to support the LV function (e.g. inotropic- and/or vasoconstricting drugs, vasodilators); if these fail to stabilize the circulation, *mechanical support* (e.g. intra-aortic balloon pump, extracorporeal mechanical circulatory support, implantable devices for cardiac support) may be considered (see below).

DIAGNOSTIC CONSIDERATIONS

Common to all shock types, *except for severe dehydration, septic shock and some other, rarer instances of distributive shock*, is that

- They often develop within minutes to a few hours after the triggering event,
- Most of the symptoms in the acute phase of shock are independent of the etiology, i.e. they are associated with the body's generalized response to blood pressure reduction, hypoxia and hypoperfusion.

SIGNS, SYMPTOMS, AND MEASUREMENTS.

Non-specific clinical signs and symptoms, well known to experienced medical and paramedical personnel (248, 249), are

- Rapid and weak (or absent) pulse.
- Rapid (or infrequent) breathing.
- Cold fingers and toes, cool, often clammy, skin over the whole body.
- Impaired mental status, ranging from fatigue to drowsiness to unconsciousness.

In addition, if the shock is caused by acute left ventricular failure or major lung embolization

- Cyanosis (not seen in severe anemia, Part 2-3) *and/or*
- Wheezing, which may be a sign of interstitial pulmonary edema ("cardiac asthma").
- Alveolar edema may accompany the above signs and symptoms.

Measurements and further investigations.

The basic tools for diagnosis of acute circulatory failure in the acute phase, available to most medical personnel also in the pre-hospital environment, are measurements of

- Heart rate (HR) and respiratory rate (RR) *and*
- Arterial blood pressure (ABP) measurements using an inflatable cuff *and*
- Arterial O_2 saturation, as measured by pulse oximetry (S_pO_2 often unreliable in shock patients).
- Diuresis may be reduced or absent during the ensuing hours.

In addition,

- Recording of the electrocardiogram (EKG) *and*
- Rapid analysis of hemoglobin (Hb) and electrolytes *and*
- Measurement of central venous pressure ((CVP) ≈ RV filling pressure in most persons) can be carried out in most emergency rooms and some emergency ambulances in the industrialized world. Under austere conditions, CVP can be measured utilizing the height of a column of sterile saline (10 cmH_2O ≈ 7.5 mmHg). For a limited time, MAP can be measured continuously by interposing a line of sterile tubing filled with sterile saline between an arterial cannula and a blood pressure measuring device.

Examinations that require specialized equipment.

In industrialized countries, the following are usually readily available within less than an hour in most acute care hospitals:

- Visualization of the heart by *echo-doppler examination*, which enables an estimation of myocardial contractility, biventricular preload, flows, pressures, and valve function.
- Measurements of *arterial and central venous blood gases* (PO_2, PCO_2, pH, and their derived parameters, supplemented by measurements of SO_2 by co-oximetry (Part 5-4) *and* blood lactate concentrations (LAC) may give information about the adequacy of O_2 supply and the lung function.
- Measurements (or estimations) of *cardiac output* (C.O.) by various methods.
- Measurement of LV filling pressure (measuring left atrial pressure (LAP) utilizing pulmonary arterial catheters (PAC)) for *calculation of PVR* is not always routinely available, reasonable approximations can be obtained by echo-doppler examinations.

In addition to the above, many well-equipped modern hospitals possess a large variety of invasive and non-invasive diagnostic apparatus of various degrees of sophistication that are available at short notice. Only methods readily available in most emergency rooms, or at the bedside in an ICU, are discussed below.

The methods for diagnosis and monitoring of circulatory parameters may be *invasive* or *non-invasive*, *intermittent* or *continuous*. The hemodynamic parameters important for both the diagnosis as well as continuous observation of therapeutic response and disease progression in a bedside setting are often lumped together as *"Hemodynamic monitoring"* – see below.

The total O_2 supply to the organism can be calculated when the Hb, S_aO_2, and C.O. are known (Part 2-3). The importance of such calculations as a guide to optimizing the DO_2 may be greatest in the initial phase of circulatory failure (see above). In the pre-hospital phase, or under austere in-hospital conditions, estimation of DO_2 may not be possible. Basic clinical observations, like the strength of pulse or ABP, HR, RR, mental state, and skin temperature become surrogate indicators, but are unreliable as *quantitative* indicators of the DO_2.

The timelines in septic shock are different from other types of shock.

While most types of shock evolve rapidly, septic shock usually develops *days* after the start of an infection. The progression from *localized infection* to *sepsis* , to *severe sepsis,* and further on to *septic shock* usually takes many hours or days. Consequently, many patients will have received substantial amounts of i.v. fluids; often also supplemented with inotropic and/or vasoactive agents, *before* they fulfill the criteria for a shock diagnosis. Sepsis *can,* however, in some instances progress from a relatively stable circulatory situation to life-threatening septic shock within a few hours, especially seen in meningococcal septicemia (250).

The initial clinical presentation may be similar in hypovolemic, obstructive, or cardiogenic shock (cold shock, see below). If resuscitation with fluids and drugs has already been ongoing for some time, patients with conditions that induce arterial vasodilation may, on the other hand, present with warm, dry skin despite continuing severe hypotension and signs of failing aerobic metabolism ((warm shock, see below, also fig. 3-30). The clinical signs and symptoms, as well as the timelines between the start of symptoms to established shock, differ with the type of microorganism, age, co-morbidity, etc. (251).

Clinical differentiation between "cold" and "warm" shock.

Cold shock. In the great majority of acute situations (the main exceptions are blood volume-compensated septic and anaphylactic shock), low blood pressure is a reflection of a low SV and reduced C.O., and therefore also of reduced flow of blood to the tissues. A constricted arterial vascular bed can, to some extent, compensate for the low SV, so that the ABP, and thus the perfusion pressure of the most vital organs, may be maintained even when the reduction in C.O. is substantial (fig 3-29). The classic picture of circulatory shock is therefore in most patients associated with the clinical signs of shock listed above and low blood pressure or weak/absent pulse; the *classical cold shock*. The magnitude of ABP reduction is, *per se* , not a very good indicator of the magnitude of reduction in C.O. (Part 3-3).

Warm shock. Vasodilation combined with low ABP in inflammatory conditions (e.g. stabilized sepsis, post hypoxic state) has been termed "warm shock". If combined with adequate preload and a normal or high C.O., the DO_2 may be normal or supernormal despite a low ABP and increased lactate levels in the blood. Other mechanisms than hypoperfusion may, however, impede aerobic metabolism in the tissues by interfering with metabolic pathways and mitochondrial function, leading to increased lactate levels (see above) *despite* adequate tissue oxygenation (see also Part 2-4).

Low ABP and circulatory shock are not synonymous.

The ABP may be reduced as a result of therapeutic interventions (e.g. vasodilating drugs, high spinal- or epidural blockades) or pathological vasodilation (e.g. high spinal injuries, reflexive vasodilation, bacterial toxins, and anaphylactic reactions). If the LV preload is maintained in the normal range *and* the coronary perfusion pressure ensures adequate myocardial oxygenation, the C.O. (and thus DO_2) may be adequate or even increased. Maintaining the preload may require infusions of substantial amounts of fluids, often supplemented with vasoconstricting agents (see Therapy below). Since the pathophysiology of circulatory shock includes a state of tissue hypoxia due to reduced perfusion (except for states where malfunction of mitochondrial mechanisms inhibit aerobic metabolism), hypotension with preserved microcirculatory flow does *not* represent a circulatory shock.

On the other hand, in patients in whom C.O. is low, but where the blood pressure is stabilized by massive activation of their sympathetic tone or by vasoconstrictor drugs, blood flow to the tissues may be reduced to critical levels. They may then develop tissue hypoxia despite satisfactory blood pressure. *Blood flow and blood pressure are not always related* (see also calculations Part 3-3); estimating the effect of therapeutic interventions on *blood flow* is far more important than focusing on increasing blood pressure.

Hypotension in the vasodilated patient.

A systolic ABP below 90 mmHg *or* a more than 30 mmHg reduction in MAP, are part of the definition of circulatory shock. Such a reductions of blood pressure do not *per se* indicate a shock state. If vasodilation reduces the SVR by 50% or more, but the preload is optimized by infusions of fluids and catecholamines, the combination of reduced afterload and increased myocardial contractility may increase the C.O. to levels where blood flow to all organs, relative to their $\dot{V}O_2$, are satisfactory or even substantially increased above normal.

Even if the flow is satisfactory, there is a lower limit for perfusion pressures. This limit, however, may vary considerably between patients. Deliberate hypotension with MAP in the 45-60 mmHg range during anesthesia, in which vasodilation is induced by drugs or central nerve blockade (hypotension anesthesia), is used during certain types of operations to reduce the hemorrhage (252, 253) and is well tolerated by patients with normal circulation. In patients undergoing operations during which a heart-lung machine replaces the pumping of the heart, MAP is often kept in the range around 50 mmHg, that is, slightly more than half of the normal value (254, 255). These procedures seldom lead to complications as a result of general tissue hypoperfusion but *may* result in local hypoperfusion if local high-grade vascular stenoses are present. A prerequisite for hypotensive procedures during spontaneuous circulation to be employed safely is that the preload of the heart, and thus the C.O., is kept at a normal (or slightly increased) level.

The limiting factors for such deliberate hypotension are *i)* the presence of localized vascular stenosis which requires a high perfusion pressure to maintain adequate tissue flow, and *ii)* the *coronary perfusion pressure* must be adequate. As the latter is determined by the diastolic ABP (DABP) minus the RA pressure, increases in RA pressure becomes more important when the DABP is low. If the DABP is around 50 mmHg and diastolic RA 5 mmHg, the coronary perfusion pressure is 45 mmHg. A rise in RA pressure to 25 mmHg reduces the perfusion pressure to 25 mmHg; i.e. a reduction of the perfusion pressure by approximately 45%. The level of RA pressure (in most patients close to the CVP) is thus important for the safety of controlled hypotension. In patients where cardiogenic shock is a result of myocardial infarction, the perfusion is limited by vascular obstruction, further limiting the tolerance to reduction of perfusion pressures in this group of patients.

The perfusion pressure within the renal cortex (the *glomerular filtration pressure*) during therapeutic hypotension may be too low for normal volumes of urinary production (e.g. in patients on a heart-lung machine, during hypotensive anesthesia). As long as the blood flow to the kidneys is sufficient to maintain adequate oxygenation and nourishment of the renal cells, normal kidneys can tolerate a low MAP for several hours; normal filtration and urine production will be re-established when the blood pressure increases after the procedure. In one case report, a patient with grave hypotension and severe oliguria for more than 48 hours after an overdose of vasodilating agent regained normal urine output when ABP was normalized (256).

TOOLS FOR EVALUATING THE CAUSE OF CIRCULATORY FAILURE

Cardiac catheterization and the pulmonary artery (PA) catheter.

Diagnostic catheterization of the heart, with measurements of the pressures within the large vessels and various chambers, started in the 1940-ties and became widely available during the following decade (257). Measurements of the O_2 content in blood samples drawn from various locations in the central circulation made it possible to chart cardiac defects and anomalies *in vivo*. For correct placement, the catheters had to be positioned under fluoroscopic guidance; the method was therefore confined to specialized laboratories.

In the early 1970-ties, a flexible catheter that could float through the right atrium and ventricle into the pulmonary artery (the PA catheter) after insertion through a large vein was developed. It was called the Swan-Ganz catheter after its two inventors (258). This catheter enabled clinicians to measure filling pressures on both sides of the heart at the bedside. Flow through the right ventricle could be measured by means of a thermosensor close to the catheter tip, using the thermodilution principle to calculate flow when a known volume of fluid with a given temperature was injected through an orifice proximal to the RA (the "CVP port"). In patients with normal central cardiovascular anatomy, the flow through the right side of the heart is representative of the C.O. This type of catheter made it possible to investigate the circulatory state in severely ill cardiac- and non-cardiac patients (e.g. septic shock, trauma patients) at the bedside; it also enabled clinicians to monitor the circulatory changes resulting from therapeutic interventions more or less continuously.

Measurements of the pressure in the RA, RV, PA, and pulmonary veins (as the occlusion pressure, PaOP or PCWP), together with measurements of the C.O., enabled calculation of the resistance in both the systemic and the pulmonary vascular beds, as well as the workload of the heart. It also offered the possibility to obtain blood samples from the PA, which is representative for the true mixed venous blood and thus enabled clinicians to estimate the relationship between DO_2 and $\dot{V}O_2$. The information obtained by use of this catheter has contributed much to what we today know about hemodynamic changes in the critically ill. Correct placement may, however, be difficult without fluoroscopy or ECHO guidance in low-flow conditions (as in most types of circulatory shock), especially when the RV is dilated. It may also precipitate arrhythmias during insertion. Advanced versions of the pulmonary artery catheter make it possible to measure both cardiac output and central venous oxygen saturation continuously, and thus provide almost instantaneous information about the effect of therapy as well as an early warning of changes in C.O. and the $DO_2/\dot{V}O_2$ ratio.

Interpretation of the obtained data requires, however, experience and a more than superficial understanding of cardiac pathophysiology. As for many other measuring devices in medicine, it is important to be familiar with the *sources of error* as well as *limitations in the interpretation* of data. Used uncritically, the results of measurements may in the worst case lead to an incorrect treatment strategy. As the shape of pressure-volume diastolic filling curves may vary substantially under pathological conditions (Part 3-1), a major source of error was created by the unreserved belief, held by many physicians at that time, that most hearts would follow the classical Frank-Starling curve, i.e. the filling pressure was representative for the correspond filling volume.

In many patients, however, and even in assumedly healthy persons, filling pressures may *not* be representative of the filling volumes, i.e. the "real" preload. In patients with increased intrathoracic pressure, cardiac tamponade, left ventricle hypertrophy or diastolic dysfunction, or in septic

hearts, the ratio between end-diastolic filling pressure and volume may be substantially altered (see diastolic dysfunction above). Measurements of filling pressures should therefore be supplemented by measurement of filling volumes (e.g. visualization with the aid of ECHO, see below). The PCWP may also be misinterpreted in patients with significant mitral insufficiency, where the pressure peak transmitted backward during systole can lead to erroneous assumptions about the LA pressure. In septic hearts, massive over-dilatation of the chambers may be seen at filling pressures that may be considered optimal for normal hearts.

Widespread use of the PA catheter during high-risk surgery and in ICUs, where interpretation of data was governed by simplified algorithms, failed to show a positive impact on patient outcomes in large studies consisting of patients with acute coronary syndromes (259, 260) or in heterogeneous groups of ICU patients (40, 41). Is use was even claimed to increase mortality (261), leading to a plea for discontinuing its use (262). Studies that concluded with no advantage of PA catheter use were, however, criticized for not having a clear protocol for the indications for catheter placement *nor* for how the data obtained should be translated into treatment goals (263). Its routine use gradually fell out of favor in the medical community; however, it still represents the only bedside method for accurate determinations of pulmonary vascular resistance, as well as for obtaining blood samples representative of the true mixed venous blood. In patients with multi-etiologic circulatory failure and cardiogenic shock who do not respond well to initial therapy, it may give valuable and rapid information about the pathophysiological state as well as the response to therapeutic interventions (264, 265).

Echo cardiography (ECHO).

With the arrival during the 1970-1980-ties of modern and mobile equipment for performing ECHO as a bedside procedure (266, 267), the dimensions and contractility of the cardiac chambers and the structure could be visualized and measured. Both changes in the degree of stiffness of the ventricular walls and the effect of intrathoracic/intrapericardial pressures often found in seriously ill patients could be identified, and a reasonably accurate estimate of the end-diastolic volume of the ventricles and the movement of the chamber walls made discrimination between systolic and diastolic dysfunction possible. In addition, Doppler signal analysis made measurements of flow and its direction possible.

While ECHO initially was the exclusive domain of trained cardiologists, modernization and increasing user-friendliness of the equipment have made it also a tool for ICU physicians, anesthesiologists, emergency physicians, ECHO technicians, and many others. It is important to realize, however, that correct interpretation of the observations requires experience and is, to some extent, subjective. The diagnostic precision of ECHO examinations as well as their interpretation depends on the skill and experience of the operator and of those responsible for the final analysis of the images.

Measurement of cardiac output.

Circulatory shock is associated with reduced C.O.; the gravity of the condition is usually reflected by the degree of flow reduction. Several methods for measurement of the C.O. exist; some can be used for continuous measurements, others for intermittent. Most of the latter can be repeated at short intervals. Methods that can be used as bedside tools can roughly be divided into four groups:

1. **Indirect calculation methods** are based on measurements of the O_2 (or CO_2) content of arterial and mixed venous blood and calculations of O_2 consumption (or CO_2 production) by analysis of the gas content of inspired and expired air (the Fick principle).
2. **Dilution of a tracer substance.** This can consist of dilution of a temperature change of the blood during passage *through the RV* (thermodilution, using a PA catheter with the sensor in the PA) *or transpulmonary dilution* (i.e. through heart-lungs-aorta, with the sensor in a major artery) (thermodilution, dye dilution, lithium dilution).
3. **Automated calculations based on the shape of the arterial pressure curve,** with corrections obtained intermittently employing dilution techniques.
4. **Direct estimation of blood flow** across the aortic valve or in the aorta (by an external Doppler probe or a probe in the esophagus suitable for continuous measurements).

In addition, blood flow in the aorta can be estimated by measurement of thoracic impedance and has been used as an alternative method by some investigators (268). See ref. (269) for an overview of the principles and technology involved in the various methods.

As the first (Fick) method requires accurate measurements of the $\dot{V}O_2$, it is best suited for use in laboratories and ICUs with considerable resources. Both the second and third methods require invasive interventions; placement of a PA catheter is considered the most invasive method. The fourth (i.e. the transthoracic approach) is non-invasive. It requires, however, personnel with specialized skill and experience and can seldom be used as a tool for minute-to-minute monitoring. Measurements utilizing the second and third methods can, however, be carried out by a trained nursing staff.

To facilitate the comparison of hemodynamic data from large and small individuals, the *indexed cardiac output* (Cardiac Index, CI) is often used. The CI is calculated as the C.O. divided by body surface area, **BSA** (CI is then given as L/min/m^2), see Apx for calculation of BSA. A person who weighs 80 kg and is 1.80 m tall has a body surface of about 2.0 m^2. The CI of a normally built adult western male is therefore close to half the C.O.

If the wall (the septum) dividing the atria and ventricles of the heart is intact, the output of the right half of the heart to the pulmonary circulation and of the left half to the systemic circulation must be equal. In the presence of cardiac septal defects, major central arteriovenous fistulae, or vascular shunts, however, only part of the output of the left ventricle will benefit the tissues of the organism. Methods for measuring C.O. that measure flow through the right ventricle (the PA catheter) may then overestimate flow into the systemic circulation. Measurement of blood flow in the descending aorta using the Doppler technique and calculation of heart function derived from the form of the arterial pressure curve (stroke volume principle) is not affected by flow through septum defects, fistula, or central shunts.

In the acute phase of circulatory shock, the C.O. will be low regardless of cause. If initial treatment fails to stabilize the circulation, C.O. measurements are important for both verification of assumptions about the circulatory state *and* evaluation of the effect of therapeutic interventions; it also makes it easier to ensure that the administration of both fluids and vasoactive drugs are kept at the lowest effective levels. In some patients, a low ABP in the initial phase after a period of myocardial ischemia and reperfusion may be due to myocardial dysfunction ("stunning", see above); on the next day, it may signify a post-hypoxic vasodilation with a high C.O. (270).

INTERPRETATION OF MEASUREMENTS AND IMAGING IN A SETTING OF CLINICAL CIRCULATORY DYSFUNCTION AND SHOCK

Non-specific parameters.

ABP is usually reduced in shock states, as the primary circulatory problem often is a low stroke volume (see above for low ABP due to other causes). In hypovolemia, it is usually well preserved until about 20% of the blood volume is lost, and the C.O. is reduced to 60% of normal (see above and fig. 3-28). Despite low SVs and insufficient DO_2, it can be normal or supernormal during extreme sympathetic stimulation, administration of high doses of alpha-1 stimulating and other vasoconstricting drugs, or to toxic doses of agents with central nervous stimulating properties. It may also be reduced in non-shock states, a low ABP does not *alone* signify a state of shock and the correlation between ABP and C.O. in shock states is poor (see above and Part 3-3).

HR and **RR** is usually increased in all types of shock, except for where it is accompanied by intracranial lesions and brainstem damage. The HR increase can be blunted or absent in patients using anti-arrhythmic drugs (e.g. beta-receptor and calcium channel blockers) or having conduction blocks requiring pacemakers; in deep shock, bradycardia may signal severe global myocardial ischemia and herald death. A rapid RR may indicate hypoxia and/or acidosis, a reduced RR may signal severe cerebral ischemia.

SpO_2 can be of value if the shock state is compounded by pulmonary failure, but is a non-specific parameter; in addition, the precision of such measurements is often poor in the shock states where the peripheral vessels are contracted. If the shock is precipitated by myocardial ischemia due to effects of toxins like carbon monoxide (CO), many of the commonly used pulse oximeters do not discriminate between HbO_2 and HbCO; the S_pO_2 value given by these may reflect the sum of both and be grossly misleading.

End-tidal CO_2 reflects the mean CO_2 in alveolar air when pulmonary ventilation/perfusion conditions are close to normal (Part 4-1). Ventilation volumes are then matched to the amount of CO_2 arriving with the venous blood; both end-tidal and arterial CO_2 is therefore stable over a wide range of variations in C.O. as well as CO_2 production. If blood flow through the pulmonary circulation is severely reduced (e.g. during shock, cardiac arrest with chest compression), the amount of CO_2 excreted to the alveoli may be below normal even if the CO_2 content of the venous blood is increased by 100% or more. If ventilation volumes are maintained in the normal range by manual or mechanical ventilation, the end-tidal CO_2 is reduced. If there is *no* flow of venous blood to ventilated alveoli (i.e. during cardiac arrest with ineffective cardiac compression), the P_ACO_2 rapidly becomes close to zero.

Reduced end-tidal CO_2 may also be due to increased alveolar dead space and/or alveoli with high V/Q ratios (Part 4-2). In major pulmonary embolism with shock (see above), alveolar dead space can be expected to increase substantially; these two mechanisms may then reinforce each other and result in a substantially reduced end-tidal CO_2.

Parameters with limited specificity.

The **Hb** concentration in the blood is important for estimating the DO_2; a low value often indicate hemorrhage as the etiology of hypovolemic shock. Before the start of fluid infusions, however, the Hb may change very little during the first 30-60 minutes despite major blood loss, as resorption of interstitial fluid is a slow process (Part 2-2). In addition, pre-existing anemia

or polycythemia cannot be ruled out based on *one* single Hb measurement; serial measurements combined with an attempt to correct for the volume of infused fluid are necessary for a meaningful estimation of the magnitude of blood loss.

EKG is equally valuable for indicating a cardiac etiology (acute myocardial infarction) as for excluding etiologies due to myocardial failure. In most patients, acute changes in the ST segment are associated with acute myocardial infarctions. A rapid sinus rhythm without ST-segment or T-wave deviations in any lead makes transmural myocardial ischemia unlikely as the primary cause of circulatory failure, but does not exclude acute valve dysfunction, ventricular septum defects or cardiac wall rupture. Endocarditis is primarily a disease affecting the valves (271, 272) and may not cause changes in the EKG directly, while myocarditis often is associated with EKG changes (273, 274).

CVP is, in most patients, representative for the RA pressure and thus an indicator of the RV end-diastolic filling pressure (**RVEDP**). A rare exception to this is patients with significant stenosis of the tricuspid valve (275), where RV filling pressures can be significantly lower than pressures in the right atrium. Insertion of a central venous line is often is necessary for securing venous access in severely ill patients, continuous or intermittent measurement of CVP is therefore easy to obtain. The interpretation of this parameter is demanding, as the relationship between RV filling pressure and –volume (RVEDV) changes with variations in RV myocardial compliance as well as with intrathoracic/intrapericardial pressures (e.g. positive pressure ventilation (see Part 3-1), positive pressure pneumothorax (see Part 4-3), pericardial accumulation of fluid or blood).

CVP may also differ considerably from the filling pressure of the left ventricle. In some conditions, especially in patients with *high pulmonary vascular resistance* caused by chronic (e.g. COPD) or acute diseases (e.g. lung emboli, ARDS), and in *acute myocardial infarction* and/or *septum defects*, the CVP may bear little or no relationship to changes in the left ventricular filling pressure. Despite increased strain on the RV resulting from elevated PA pressures during the first phase of acute ischemic LV failure, the CVP may stay normal or only modestly increased for several hours as long as the RV is able to cope with the increased workload.

In a large group of unselected ICU patients with indwelling PA catheters, the correlation between filling pressures (*either* CVP *or* PCWP) and the indexed C.O. was extremely poor (fig 3-31). Due to such lack of relationship, normal or even increased CVP does not exclude hypovolemia or reduced diastolic filling due to other causes.

Despite the potential pitfalls in using filling pressures as surrogates for filling volumes, a low CVP in a patient in clinical shock indicate reduced venous return, i.e. hypovolemia or pathological vasodilation can be assumed to be *part* of the circulatory problem. Increasing the venous return by increasing the circulating blood volume by rapid volume infusions can then be expected to have a beneficial effect, and a trial infusion of fluid is warranted. On the other hand, a very high CVP pressure may indicate that the RV already has problems with propelling the venous return through the lungs and into the LV, *or* that increased intrathoracic or intrapericardial pressures impedes diastolic filling of the heart (see fig. 3-15).

Pulmonary artery pressure (PAP) is normal when the pulmonary circulation and the LV can accommodate the output of the RV. As the normal pulmonary vascular bed is highly compliant, an *increase* in C.O. does not increase the PAP to the same degree unless the compliance or resistance of the pulmonary vascular bed is changed. Thus, a modestly increased PAP may be due to a high C.O., a very high PAP indicates *either* a primary increase in PVR, *or* an increase in

LVEDP that is transmitted back through the pulmonary circulation, *or* both. It may also be a result of mitral valve stenosis. On the other hand, if the output of the RV decreases while the LV function remains normal (e.g. primary RV myocardial dysfunction, or secondary to low venous return), the PAP can be normal or reduced. As the C.O. is reduced, the calculated PVR may be increased even when PA pressures are normal.

The left atrial pressure **(LAP)** is an indicator of the LV filling pressure. In most situations, the pulmonary artery occlusion- or capillary *wedge* pressure (PAOP, PCWP), obtained utilizing a catheter wedged in a branch of the PA, is representative of the LAP. As for the CVP, the relationship between LV filling pressures (LVEDP) and –volumes (LVEDV) may deviate substantially from that considered to be in the normal range; the correlation may be extremely poor especially in patients with diastolic dysfunction and mitral valve stenosis or insufficiency. Nevertheless, as for CVP above, low pressures indicate a low preload and very high pressures in the absence of increased intrathoracic/intrapericardial pressures indicate that increasing the blood volume by rapid fluid infusions is unlikely to have a beneficial effect on cardiac function.

After acute rupture of a mitral papillary muscle and sudden development of massive mitral regurgitation, part of the LV stroke volume will be propelled backward into the pulmonary veins. The PCWP then shows a pressure wave that *resembles* a normal PAP but the *peak* is *delayed* relative to the true PAP and ABP waves. As for CVP, the correlation between PCWP and the indexed C.O. in a mixed population of intensive care patients proved to be extremely poor (fig. 3-31).

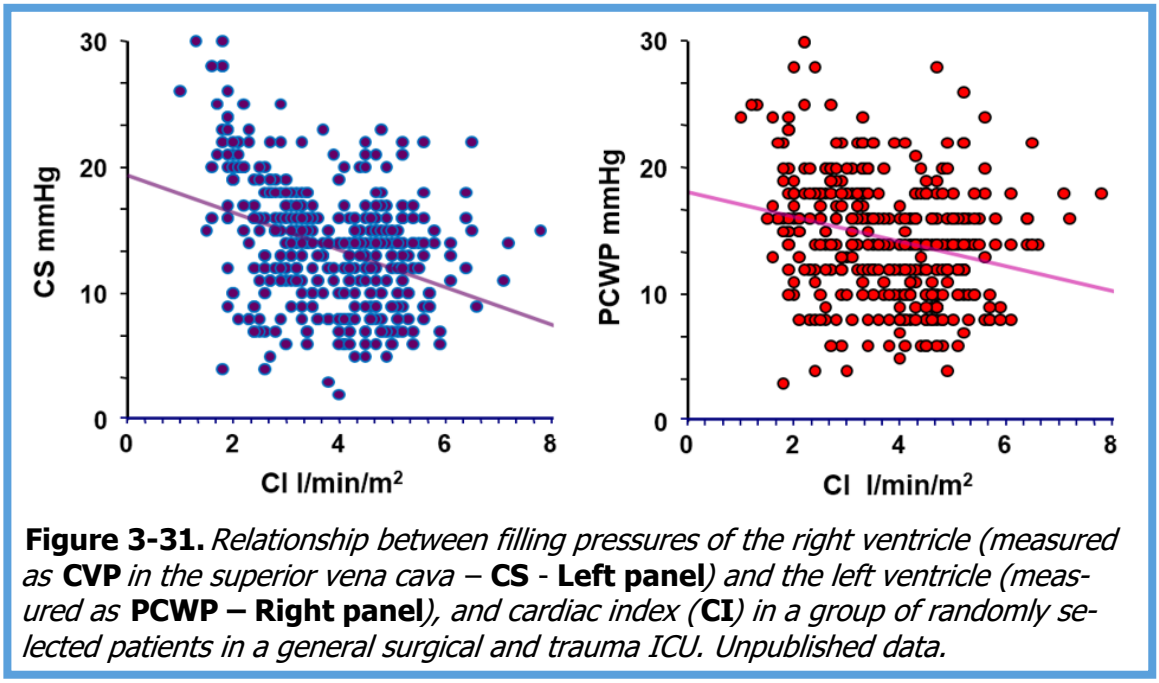

Figure 3-31. *Relationship between filling pressures of the right ventricle (measured as* **CVP** *in the superior vena cava –* **CS** *-* **Left panel***) and the left ventricle (measured as* **PCWP – Right panel***), and cardiac index (***CI***) in a group of randomly selected patients in a general surgical and trauma ICU. Unpublished data.*

Parameters with satisfactory specificity.

Measurements of C.O. (see above) have a good specificity for discriminating between hypotension caused by low C.O., and reduced ABP due to other causes (e.g. arterial vasodilation, see above). Determining the underlying cause of shock in patients who do not respond well to therapy and where the cause is difficult to define can be done utilizing a combination of a PA catheter and ECHO (see below) supplemented with the arterio-venous C_aO_2 and PCO_2 difference. The combination of knowing the filling pressures, filling volumes, myocardial contractility and valve function on both sides of the heart can pinpoint the mechanism precipitating a central circulatory

failure in most patients but cannot always reveal the cause of non-ischemic myocardial dysfunction.

ECHO is readily available in the emergency room and bedside anywhere in most hospitals in the industrialized world; simple and rapid estimations of left and right ventricle end-diastolic volumes (LVEDV and RVEDV, respectively, see below), myocardial contractility, and valve function, can often be carried out using the non-invasive transthoracic ECHO technique. This approach, however, do not give sufficient visualization of the heart in all patients. Transoesophageal ECHO usually offers better visualization, but represents additional stress in awake critically ill patients. In already intubated and sedated patients, transesophageal examinations have few contraindications.

- **RVEDV** visualization gives information about the RV filling volumes. A small RVEDV is compatible with hypovolemia, vasodilation, or external compression of the large central veins and/or the chambers of the right heart. An increased **RVEDV** is compatible with primary or secondary RV failure (see above). If the LV is similarly affected, the cause is usually RV failure secondary to high PA pressures transmitted backward from high left atrium pressures.
- **LVEDV** visualization gives information about the LV preload. As for RVEDV above, a small **LVEDV** is compatible with hypovolemia, vasodilation, or external compression of the large central veins and/or the chambers of the right heart, but also with increased resistance in the pulmonary circulation (e.g. major pulmonary embolization) or compression of the left atrium. In the latter cases, fluid infusions may not solve the problem (see therapy). An increased **LVEDV** is compatible with LV failure, but may also represent a chronically dilated heart.

The calculation of a reduced **EF** is often misinterpreted as being synonymous with a reduction in SV and work capacity of the heart. While an important prognostic parameter in chronic heart failure, it changes with end-diastolic pressures (see also fig. 3-5). If the LVEDV is increased by 60% and the SV by 30%, the calculated EF is reduced by 20% despite the supernormal SV. The interpretation of EF is especially difficult in the septic heart; patients with hearts that show an increased LVEDV, and thus a reduced EF, had increased survival rates in one study, and the LVEDV normalizes within 1-2 weeks in survivors (163).

MRI and **CT** are also excellent methods for the evaluation of cardiac function. In many, but not all, western hospitals this type of imaging is available within minutes after arrival at the hospital; further resuscitative efforts and interventions may, however, be hampered by such examinations while ECHO examinations can be carried out simultaneously with other interventions.

Laboratory analyses in the diagnosis of circulatory shock.

Sampling sites for blood to analysis (see also Part 5-4).

The arterial-venous difference in SO_2 and PCO_2, as well as changes in blood lactate levels, can give important information about the gravity of circulatory failure (see below). Blood samples drawn from a central venous catheter (CVC) are often used to estimate such differences. This is useful for rough qualitative assessments, but *accurate* calculations of the SO_2 and PCO_2 a-v differences require access to samples of arterial and mixed venous blood. The latter *must* be taken from deep into the right ventricle, or preferably from the pulmonary artery, to be representative

As few patients have PA catheters, blood samples from the superior vena cava or other intrathoracic veins are often used as surrogates for true mixed venous blood. In most patients, this practice may allow *qualitative* conclusions about the relation between the $\dot{V}O_2$ and DO_2 to be drawn, the *quantitative* error in the individual patient is, however, of unknown proportions (fig. 3-32, see also below). As the ability to utilize O_2 may change as a result of both toxic agents and disease (Part 2-4), the results must be integrated with both clinical observations and other laboratory results to give an accurate picture.

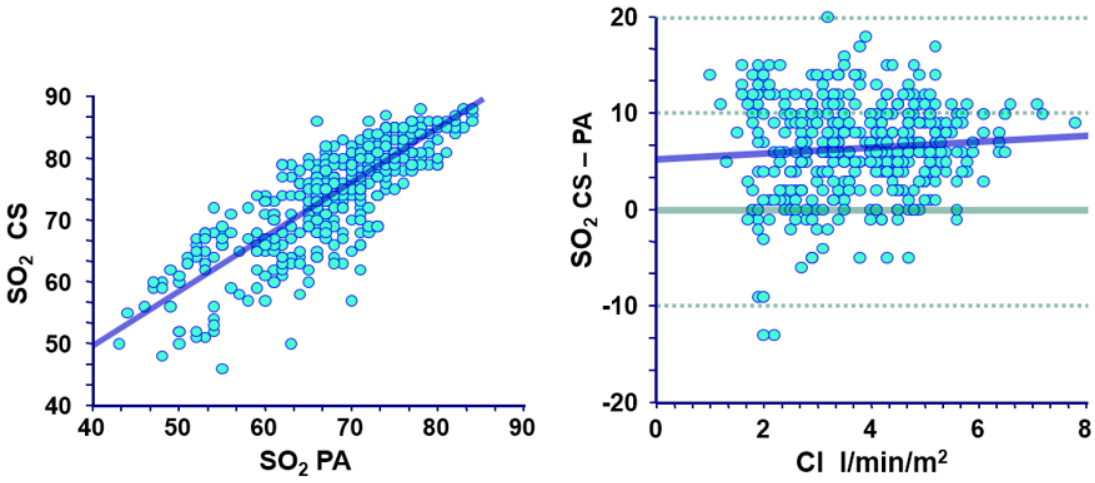

Figure 3-32. *O_2 saturation* (**SO_2**) *data from a group of randomly selected patients with an indwelling PA catheter in a general surgical and trauma ICU.* **Left panel: SO_2** *values in samples obtained simultaneously from the superior vena cava* (**CS**) *and the pulmonary artery* (**PA**). **Right panel:** *The same data shown as the* **CS-PA SO_2 difference** *as a function of the cardiac index* (**CI**). *Unpublished data.*

The blood in the superior vena cava has normally a slightly lower oxygen saturation than the blood in the inferior vena cava. If the oxygen saturation of blood from the pulmonary artery is significantly higher (> 5-8%) than that in the superior vena cava, a left-to-right leakage of blood through a septum defect or major vascular anomalies may be suspected, and if so must be verified with the aid of an ECHO-Doppler examination.

Lactate levels, measured in either venous or arterial blood in patients, are similar (276). Many modern blood gas analyzers measure lactate along with blood gases, electrolytes, and other blood chemistry parameters. Increased lactate may be an indicator of tissue hypoxia; however, it may also be a result of intense muscular activity, high levels of adrenaline, and other non-shock conditions.

Mixed venous O_2 saturation and cardiac output.

According to the Fick equation, the O_2 content of the mixed venous blood reflects the difference between the DO_2 and $\dot{V}O_2$. The former is determined by the C.O. and the C_aO_2, the latter varies with the metabolic activity (e.g. muscle activity, body temperature, catecholamine levels, thyroid hormones, degree of sedation, mitochondrial function). In clinical medicine, this connection has sometimes been used to draw conclusions about the C.O. based on the SO_2 in mixed venous samples, or in samples obtained from a central vein. As illustrated by the distribution of SO_2 values relative to CI in fig. 3-33, such conclusions have a high degree of uncertainty. Unless levels in Hb, C_aO_2, and $\dot{V}O_2$ are included in the calculations, the quantitative precision of such a practice is poor.

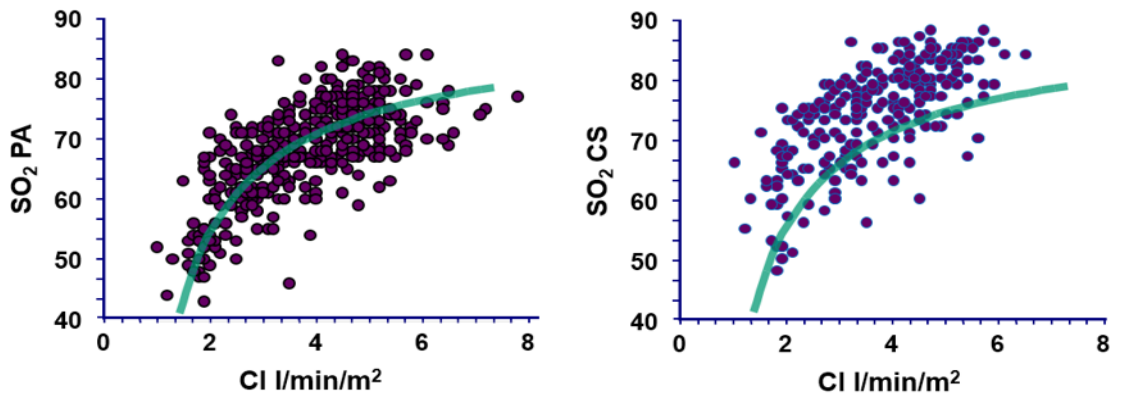

Figure 3-33. Left panel: *Venous O_2 saturation* (**SO_2**) *values in blood samples from the pulmonary artery* (**PA**), relative to cardiac index (**CI**), *in a group of randomly selected patients with an indwelling PA catheter in a general surgical and trauma ICU. The* ***green curve*** *represents mixed venous* SO_2 v*alues calculated for the same mean Hb if the O_2 consumption is normal.* **Right panel:** SO_2 v*alues in samples obtained simultaneously from superior vena cava* (CS) *in the same patients, green curve as in the left panel. Unpublished data.*

The S_vO_2 value in blood from any central vein is, however, valuable as an initial screening; a low value in a patient with a close to normal calculated C_aO_2 should lead to further investigations of the hemodynamic state of the patient. On the other hand, an increased S_vO_2 value does not always rule out a low C.O. (e.g. mitochondrial dysfunction, left-to-right cardiac shunts). Variations in mixed or central venous oxygen saturation (S_vO_2) taken sequentially from the same patient represent a semi-quantitative indication of *variations* in C.O. if the C_aO_2 remains stable. Used as such, they may give information about whether the effect of efforts to increase C.O. (by infusion of fluid, inotropes etc.) has the desired effect.

Arterio-venous O_2 saturation difference (a-v SO_2).

The calculated S_aO_2 - S_vO_2 difference, when corrected for the current Hb (the simplified C_aO_2) as well as for body temperature, has a better precision than S_vO_2 alone and may be used to confirm C.O. measurements qualitatively. As patients in circulatory shock often have acid-base, electrolyte, and ventilation disturbances with shifts in the HbO_2 dissociation curve, the O_2 saturations must be analyzed in a co-oximeter and not calculated

Arterio-venous CO_2 difference (a-v PCO_2).

If the production of CO_2 in the tissues is normal or increased, but the blood flow is reduced, each unit of blood passing through the microcirculation absorbs more CO_2 per ml than normal. The venous PCO_2 is then increased. On the other hand, the reduced venous flow to the alveoli (pulmonary hypoperfusion) may reduce the total amount of CO_2 reaching the alveolar space per minute. If pulmonary gas exchange function (i.e. V/Q ratio, Part 4-1) is intact, and minute ventilation is normal or increased, the P_ACO_2 may be normal or decreased, in which case the P_aCO_2 changes in the same direction. Arterial (and end-tidal) CO_2 levels may then be normal or low, while those in mixed venous blood may be increased to levels 50-100% above normal (277, 278).

Important confounding factors in a-v SO_2 measurements.

Mitochondrial dysfunction is sometimes designated as *cytotoxic shock.* The presence of endogenous (e.g. metabolic changes induced by bacterial toxins or inflammation mediators) or toxic exogenous agents (e.g. cyanide, hydrogen sulfide, sodium azide) that inhibit or block mitochondrial utilization of O_2 may cause S_vO_2 values to be unexpectedly high despite a low C.O. In shock states of many hours duration, the $\dot{V}O_2$ may be reduced due to hypoxic mitochondrial damage (Part 2-1); the interpretation of an increased S_vO_2 value may then be ambiguous.

Atrial or ventricular septum defects with left-to-right shunts result in high SO_2 in samples from the PA when oxygenated blood from the left side of the heart becomes mixed with venous blood from the right half. Also, certain anatomical vascular anomalies (279) may have a similar effect. If the defect is on the atrial level, blood drawn from a central line with the orifice situated deep in the SCV or the right atrium may also be increased. When septum defects are on the ventricular level, the SO_2 in samples from the right ventricle or pulmonary artery are increased, while samples drawn from a central vein have a substantially lower SO_2.

THERAPEUTIC GOALS AND OPTIONS IN CIRCULATORY FAILURE AND SHOCK

General goals

Regardless of the situation and the cause of the circulatory problem, a close to normal S_aO_2 and a corresponding P_aO_2 should *always* be a high-priority goal in the hyper-acute phase. Substantial reductions in C_aO_2 due to either a Hb reduction to 33% of normal (50) or a S_aO_2 reduction to 55-60% of normal (280, 281) can be tolerated in well-trained healthy persons with a normal cardiac reserve for a limited time (Part 2-3); similar reductions in patients with limited cardiac reserve capacity may, however, result in severe tissue hypoxia and be lethal. Achieving *normal* (or supernormal) values for global O_2 supply in severely ill persons, however, should *not* be a goal *per se,* but a high P_aO_2 may be indicated in some conditions (see O_2 Therapy below).

What *degree* of reduction in O_2 delivery that should be considered acceptable in a severely ill patient is difficult to determine, and may vary between individuals as well as within patients with similar circulatory problems. The lower acceptable limit of DO_2 is not easily defined; scientific data describing findings in animal experiments and investigations in ICU patients (282) may not be relevant for conditions during the hyper-acute phase.

Also, the goals to strive for in the first minutes to a few hours after circulatory collapse are not necessarily the same as those that should be pursued when some degree of stabilization has been achieved and/or the underlying processes have been identified and remedied. The availability of resources (e.g. equipment, human- and transport resources, distance to hospital, resources at the nearest hospital, and transport distance to specialized resources) may also have an impact on the here-and-now therapeutic focus.

The benefits of attempting to optimize the circulation, and thus the DO_2, to normal (or supernormal) values, probably depend on the stage of disease. When the patient is in the acute phase (e.g. under surgical procedures, where the patient is already monitored, and rapid adjustments can re-establish normal oxygenation within a minutes) or in ongoing shock, the effect of interventions may have a larger impact than during a stabilized postop/ICU phase where extensive cellular damage may already have occurred. Early re-establishment of adequate circulation and optimizing DO_2, before tissue hypoxia and/or signals released by bacterial toxins or other inflammatory processes have induced changes in the cellular metabolism, can reduce organ failure and

mortality (283, 284, 285). There is, however, no compelling evidence that interventions instituted to optimize circulation of patients well into the ICU phase, after organ dysfunction or failure has been established, has a positive impact on morbidity or mortality (286).

Therapeutic interventions.

The success of therapeutic interventions aiming at stabilizing a failing circulation depends on whether assumptions about the underlying processes are correct. Acute circulatory failure may have many causes, as detailed in Part 3-2 and Part 3-3. The choice of the *initial treatment strategy* depends on the diagnosis, or the clinician's *assumptions* of whether the failure is primarily due to

- **Hypovolemia** (i.e. decreased venous return due to reduced blood volume).
- **Pathological vasodilation** (i.e. decreased venous return with normal blood volume but with reduced vascular tone and/or reduced arterial resistance).
- **Obstruction of blood flow** in the pulmonary vascular bed (e.g. embolization).
- **Changes in cardiac function**, i.e. myocardium contractility or compliance, valve function, heart rate, or mechanical properties.
- **External factors** that impede the normal filling of the heart (e.g. high intrathoracic or intrapericardial pressures).
- **Increased afterload** (e.g. acute blood pressure increase, acute valve obstruction).

or to *any combination* of the above.

Appropriate therapeutic options can roughly be grouped into

- **Supportive interventions** that are directed towards maintaining a DO_2 compatible with aerobic metabolism until specific therapeutic interventions (if available) can be carried out.
  - **Traditional supportive interventions** (e.g. administration of supplemental O_2, assisted or controlled ventilation, infusion of fluids, blood products, vasoactive and inotropic drugs) are available in most hospitals and many pre-hospital settings in the industrialized world.

  If these fail to stabilize the circulation, they can be supplemented with
  - **Advanced supportive interventions** (e.g. external and internal mechanical devices that support the cardiac function); such options are usually available only in larger or specialized hospitals.
- **Specific interventions** that are directed towards correction of the underlying problem (e.g. surgical or radiological repair of skeletal or cardiovascular injury, removal of emboli, clots, or other sources of vascular occlusion in the central circulation, infusion of thrombolytic agents, administration of antidotes to toxic agents or drug overdoses) whenever appropriate and possible.

When treatment directed towards the assumed cause of the problem fails to improve the condition of the patient, or occasionally makes matters worse, more information is needed to confirm or refute the initial diagnosis.

Conventional supportive interventions – an overview (fig. 3-34).

A. Increase the F_iO_2 ① to avoid or minimize hypoxemia.

B. Optimize preload. If *low LV preload* is suspected, increased transcardiac pressures may restore the preload using infusion of f**luids/blood** products ② and **vasoconstrictors** ③ (short term only) to **increase venous return** and **increase RV preload** ④. The *assumption* that increased RV stroke volumes will also increase the diastolic LV filling ⑤ is valid in most, but not

all (e.g. major PE) patients. Removal or reduction of increased extracardiac pressures (**ECP**, - e.g. reduce CPAP/PEEP, see below) may enhance the LV filling in hypo- or normovolemia. Any combination of fluid, vasopressors, and inotropes aim at securing a C.O. compatible with a level of DO_2 that makes aerobic metabolism possible in all tissues ⑥.

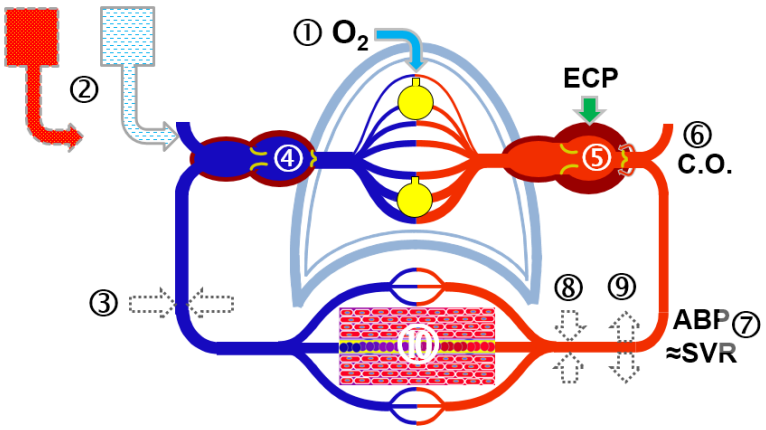

Figure 3-34. *Schematic overview of traditional supportive interventions in acute circulatory failure. See text for explanation and symbols.*

C. Secure adequate perfusion pressure (ABP) ⑦ by using ⑧ vasoconstrictors or ⑨ vasodilators to keep an adequate microcirculatory flow ⑩ while simultaneously minimizing the resistance to LV ejection. **NB**: If primary cardiac failure can be assumed to be the primary etiology, inotropic support may represent the *second* step after O_2 administration.

SUPPLEMENTARY OXYGEN IN CARDIOVASCULAR FAILURE.

Avoiding hypoxemia by administration of supplementary O_2, progressing to ventilation support when indicated.

The rationale for increasing the F_iO_2 is *either* that

- The P_aO_2 *or* the S_aO_2 *or* both are subnormal (i.e. S_aO_2 < 95%), *or* that
- Severe anemia is present, or may be assumed from the clinical situation*, or* that
- Intoxication with carbon monoxide is suspected.

Regardless of the etiology of circulatory failure, any reduction in C.O. causes a proportional reduction in D_aO_2 (Part 2-3). An important goal is therefore to avoid a simultaneous reduction in C_aO_2, which may tip the D_aO_2 below the critical range for local or generalized hypoxia.

In circulatory failure patients with normal Hb levels, supplying additional O_2 to the inspired air can be expected to be beneficial if the S_aO_2 is reduced to levels below 94-95%; in most clinical settings, aiming for a supernormal P_aO_2 if the S_aO_2 is already adequate has not been proven useful. Administering 100% O_2 may even have negative effects on lung function; atelectasis may form within a few minutes in patients breathing with small tidal volumes (see Part 4-4) and inflammatory changes in the airways may be detected after several hours to a few days (see Part 2-1, oxygen toxicity).

Despite these caveats, supplementary O_2 *should* be given to increase F_iO_2 in acute circulatory failure states, especially when reliable measurements of $S_PO_2/S_aO_2/P_aO_2$ are not available. The period for administering 100% O_2 should always be as short as possible. As soon as reliable S_aO_2 or S_pO_2 measurements can be made, the F_iO_2 should be titrated to obtain the desired SO_2 levels. A reduction in F_iO_2 from 1.0 to 0.5 greatly reduces the negative effects of supplemental O_2. If pulmonary shunting is the primary problem, as it often is in acute respiratory failure, the difference in effect on C_aO_2 between these two levels is small (Part 4-4, fig. 4-28 and 4-29).

Positive pressure ventilation in circulatory failure.

If increasing the F_iO_2 fails to secure satisfactory levels of P_aO_2 *or* S_aO_2, interventions aiming at increasing the total alveolar-capillary interface and/or increasing the alveolar ventilation may be necessary. The former may be achieved by increasing the mean and the end-expiratory airway pressure, the latter by mechanical assisted or controlled positive pressure ventilation. Applying positive pressure to the airways may have negative effects on the C.O., especially if reduced LV diastolic filling already is part of the circulatory problem. Positive airway pressure can be applied during spontaneous ventilation, assisted- or controlled ventilation (see Part 4-4 for methods).

The *rationale for applying positive pressure ventilation* may be

- Positive airway pressures are necessary to increase the alveolar-capillary gas exchange surface to an extent where oxygenation of the blood can be secured without the use of very high F_iO_2 levels.
- Insufficient ventilation volumes, i.e. the supply of fresh O_2 to the lungs during inspiration, is too low to maintain a satisfactory P_AO_2 and thus arterial blood oxygenation.
- Insufficient ventilation leads to substantial CO_2 accumulation and severe respiratory acidosis.

If applying CPAP or IPPV interferes with diastolic filling and reduces the C.O. further, one of the body's most important compensatory mechanisms in threatening oxygenation failure (see above) is inhibited. In some situations, the objective of improving gas exchange in the lungs and securing a satisfactory C.O. will therefore be in conflict with each other.

Patients with acute respiratory or cardiac failure usually have a strong reflex stimulation of the sympathetic nervous system with high endogenous catecholamine production, leading to vasoconstriction and increased vascular resistance. Anxiety and pain (shortness of breath, pain in acute myocardial infarction) increase catecholamine production still further. In addition, patients with chronic heart failure often have a reduced blood volume due to continuous stress-induced contraction of the vascular bed (287). Removing the sympathetic stimulation by deep sedation in connection with endotracheal intubation for positive pressure ventilation may lead to dramatic decreases in blood pressure in such patients. This can occur even when the drugs employed do not by themselves cause significant vasodilation or cardiodepression (e.g. ketamine). Non-invasive ventilation may then be preferable in the initial phase (see also Part 4-4).

FLUIDS IN CARDIOVASCULAR FAILURE.

Optimizing preload by rapid infusions of fluid.

Fluid infusions are usually the *second therapeutic intervention*, except for in patients with cardiogenic shock with signs of severe cardiac insufficiency (e.g. massive venous stasis, frank pulmonary edema). In those, expanding the blood volume by administration of i.v. fluids when the LV is already dilated may aggravate the cardiac failure, especially in the presence of functional mitral insufficiency (see above). It may also increase pulmonary edema and hypoxemia.

Depressed cardiac function due to **reduced end-diastolic volume** caused by hypovolemia is initially treated by autotransfusion (raising the legs, inclining the patient with head downwards) followed by intravenous fluid administration. If the hypovolemia is due to hemorrhage, blood transfusions (see also Part 2-4) may also be necessary to maintain the oxygen transport capacity of the blood.

The *rationale for expanding the blood volume* by rapid infusion of fluids in patients with acute circulatory failure rests on the assumption that

- At least *part* of the circulatory problem is due to sub-optimal LV diastolic filling, *and*
- Increasing the venous return will increase the RV stroke volume and subsequently the LV end-diastolic filling volume, *and*
- The LV will respond in accordance with the Frank-Starling mechanism and increase the C.O.

In addition, keeping the atria well filled may reduce the tendency for atrial fibrillation (288). The effect of fluid infusions constitutes an important feedback loop – if the clinical condition improves, the assumption about suboptimal LV filling volumes may be considered verified.

Conditions that satisfy the rationale above are

- All conditions where LV failure is *secondary* to reduced venous return and RV filling insufficiency (e.g. major hemorrhage, acute vasodilation. acute loss of fluids, severe dehydration.
- Conditions where reductions in preload of one or both ventricles is caused by significant increases in the airway- and/or intrathoracic pressure (reduced transvascular and/or transcardiac diastolic pressures).
- Conditions where increased preload is necessary to optimize cardiac function.

An isolated reduction in LV filling (e.g. obstruction of blood flow through the pulmonary circulation) may also benefit from fluid infusions. The infusion must in such instances be titrated carefully; if the RV is already in failure and grossly dilated, aggressive fluid infusions may dilate the RV further and aggravate the LV failure by reducing its end-diastolic volume even more (Part 3-1, Ventricular interdependence).

In circulatory failure due to sepsis, reduced venous return, myocardial dysfunction, and reductions in arterial vascular resistance often co-exist (Part 3-2). Maintaining an adequate C.O. may require increased preload and raised diastolic filling pressure, which again increases hydrostatic pressures in the capillary bed. The price of optimizing cardiac function is then increased tissue edema, which increases the distance between capillaries in the tissues and thus the distance between erythrocytes and tissue cells. This *may* reduce the O_2 supply to tissue cells in patients with severe hypoxemia (289).

Finding the optimal balance between infusion of fluids to optimize the preload, and simultaneously avoiding increased hydrostatic pressures in the microcirculation, can be very difficult. A combination of i.v. fluids, vasopressors, and inotropes (see below), combined with continuous monitoring of the circulatory effects of the interventions and correct interpretation of the results, are necessary to optimize the process. Such optimization does not guarantee that the desired balance *can* be achieved; tissue edema can seldom be avoided in patients with increased capillary leakage who need an increased preload for adequate cardiac function.

Types of fluid and effect on blood volume expansion.

Many types of intravenous fluids have been used as plasma volume expanders. The ideal infusion fluid for volume expansion in acute circulatory failure should

i) Remain within the circulation for hours,
ii) Have no negative effects on the coagulation, the immune systems, metabolism, etc.
iii) Be eliminated by the kidneys without leaving foreign macromolecules in the interstitial fluid.

Such an ideal fluid does not exist; iso-oncotic albumin solutions may be closest to the requirements above, but have not been proven superior to other alternatives (see below). Some of the fluids in common use today, and during the last decades, are described below.

A. Fluids that are iso-osmolar *and* **iso-oncotic** with plasma, and are expected to remain intravascularly for some hours under normal conditions.

Blood products.

Whole blood (WB) and **fresh frozen plasma (FFP)** are close to isotonic and iso-oncotic with the circulating blood; FFP also contains all normal plasma proteins including the coagulation factors. **Erythrocyte concentrates** (packed red blood cells) are *not* iso-oncotic. Blood products are expensive, of limited supply, and require storage under well-controlled conditions. In addition, blood products occasionally cause generalized immunological and/or localized pulmonary reactions (Transfusion Related Acute Lung Injury - TRALI (290, 291))(Part 2-3). The indications for elective transfusion of blood products have become increasingly stringent during the last decades; in acute situations with unstable circulation (e.g. severe trauma, acute, massive hemorrhage due to other causes) the indications are more liberal.

Stored plasma is also isotonic and iso-oncotic, but contains reduced contents of coagulation factors. Most of the coagulation factors may, however, be preserved in plasma in which microorganism inactivation is accomplished through a special process.

Albumin solutions.
The rapid loss of infused crystalloids from the intravascular space (see below) led to attempts to reduce such fluid leakage by using "physiological" plasma expanders, making crystalloid solutions iso-oncotic or hyperoncotic by adding human albumin. The use of such solutions is debated. A Cochrane study published in 1998 concluded that albumin infusions had no benefits in critically ill patients and might even be harmful (292); despite a storm of criticism from various sources this conclusion was later upheld but without the assumption of harmful effects (293). A large study on the use of albumin in sepsis also failed to show a significant benefit on 28- or 90-day mortality in the patients (294), even if a modest positive effect in the most severely ill patient group could be found.

Artificial colloids. In an attempt to make iso- or hyperoncotic solutions cheaper and more available, various types of artificial macromolecules (e.g. gelatin, dextrans, hetastarches) have been added to crystalloid solutions to increase the oncotic pressure of the fluid ("colloids") and thus manipulate the Starling forces in the microcirculation. Such solutions played an important role as i.v. plasma expanders over several decades. Even if fluids containing artificial colloids stay longer in the circulation (295), they do not seem to confer any advantage over pure crystalloids when it comes to survival or the total amount of fluid infused (296). As their use also was associated with various complications (297), the use of artificial colloids as plasma volume expanders during acute hemorrhage or vasodilation has been questioned. A Scandinavian expert group has recommended that such fluids should no longer be used routinely (298).

Albumin solutions are now the only colloid that is recommended for volume expansion in the critically ill (299); a combination of crystalloids and colloids is recommended by some experts when large volumes of i.v. fluids are necessary (300). Some investigators still report a positive effect of albumin use (301); the pros and cons of the use of albumin solutions as plasma expanders are still debated (302, 303).

B. Crystalloids: Fluids that are iso-osmolar with plasma, and where the effect on intravascular volume expansion is attenuated within minutes to hours.

Fluids consisting of water to which electrolytes and other small molecules (lactate, acetate) are added to make the fluid iso-osmolar with plasma and interstitial fluid are named *crystalloids*. Two types of isotonic crystalloid solutions in common use are **Ringer's Lactated** or **Acetated solution** and **Isotonic Saline** (NaCl 0.9%, also called *Normal* Saline). The Ringers solutions contain less Na^+ than the plasma and ICV (130 mmol/l *vs* 142 mmol/l) but the Cl^- and K^+ content is similar. NaCl 0.9% contains slightly more Na^+ than plasma (154 vs 142 mmol/l) and may lead to hypernatremia if large quantities are infused. The Cl^- content is equal to the Na^+ and thus about 50% higher than the plasma and there is no K^+ in the solution.

Ringer's lactated solution may increase the blood lactate levels. This effect is modest; as it contains ≈ 30 mmol/L lactate, which is rapidly distributed to both the extra- and intracellular space, each liter of this solution will increase the lactate levels in the blood of a 70 kg person by less than one mmol/L. As lactate (the conjugate base, Part 5-1), and not lactic acid is infused, it will not aggravate an acidosis in a patient. The acetated version does not add lactate to the organism; under aerobic conditions, both lactate and acetate are metabolized by the tissues.

The other commonly used crystalloid, **isotonic (0.9%) NaCl**, may induce hypernatremia and hyperchloremic acidosis if given in large quantities (304, see also Part 5-3). Switching between Ringer's and NaCl in a roughly 2:1 proportion, should theoretically minimize the drawbacks of both of them.

The intravascular volume expansion by crystalloid infusions is difficult to predict. In *normal volunteers*, about 50-65% of the infused volume is still in the circulation at the end of a 60 min infusion of 1000 ml Ringer's acetate. Two hours later, only 20-30% of the infused volume is still in the circulation (305). The rest of the infused volume has entered the interstitial space. If large volumes of crystalloid solutions are infused, the capacity for lymphatic drainage may be exceeded and tissue edema occurs.

As expected from the Starling forces in the microcirculation, the speed of extravasation changes with the hydrostatic pressures in the microcirculation. Hypotension reduces the speed of extravasation; on the other hand, inflammatory changes in the microcirculation (capillary leak) increase it.

A 5% solution of glucose (DW 5%) in water is also isotonic with plasma *before* infusion but is *not suitable* as a blood volume expander. When the glucose is metabolized, the water enters both the extracellular and the intracellular space, leaving only a small part of the infused volume in the circulation.

C. Fluids that are hyperosmolar and/or hyperoncotic relative to plasma.

Hyperosmolar fluids will, after leaving the microcirculation and entering the interstitial space, increase the osmotic pressure outside the cells and mobilize intracellular fluid into the interstitial compartment. Part of the increased interstitial fluid volume then flows back into the intravascular compartment. Such a strategy has two theoretical advantages: ***i)*** The total amount of exogenous water entering the body is smaller and can be infused faster, and ***ii)*** the amount of fluid that needs to be transported/stored under austere conditions is smaller. In addition, cell edema (especially in the brain) can be counteracted; reduced activation of immunologically active cells has, however, been reported.

The positive effects last, however, only as long as the difference in osmolarity between the intra- and extracellular fluid persists. Despite the theoretical advantages and positive results in small

studies, a favorable effect of hyperosmolar fluids in circulatory failure, compared to isotonic fluids, could not be proven in larger studies (reviewed in ref. 306).

Expanding the intravascular volume by infusion of fluids may reduce the Hb, and thus the C_aO_2. The tolerance for Hb reduction is, however, great in persons with normal cardiac capacity (Part 2-3); as long as the fluid infused has a positive effect on LV preload and re-establishes the heart's capacity for increasing its output, the *net* effect on DO_2 is often favorable.

Making *general recommendations* about fluid therapy and interpretation of measured parameters in severely ill patients is difficult. Patients in acute "here-and-now" circulatory failure, and patients in which attempts at stabilization have been ongoing for several hours – or days, represent two different populations. Extrapolating results from scientific investigations carried out in one population to the other may be counterproductive.

DRUGS FOR USE IN ACUTE CARDIOVASCULAR FAILURE.

A multitude of drugs affects the function of the cardiovascular system. Many of them are primarily intended for oral treatment of hypertension, chronic heart disease, or arrhythmias; some drugs used in treatment of non-cardiovascular diseases also affect the heart and circulation. Even if many of these drugs (especially those used to treat hypertension) have been shown to reduce long-term morbidity and increase survival, long half-lives make most of them unsuitable for use in emergencies.

This compendium focuses on drugs suitable for i.v. administration and support of the cardiovascular function in acute situations, where circulatory failure (i.e. reduced C.O., low perfusion pressure, or both) threatens the O_2 delivery to the tissues. Such drugs may prevent cardiovascular collapse on a here-and-now basis and buy time for other therapeutic interventions to become effective, their effect on long-term mortality is, however, uncertain. A list of some of the drugs commonly used in clinical medicine for treatment of patients with acute circulatory failure is presented in table 3-2.

The choice of vasopressors, inotropes, and vasodilators are, in the initial acute phase, often guided by *assumptions* about the pathophysiological changes in the individual patient. Such assumptions do not always prove to be true; initial therapeutic choices may need to be re-assessed when more information become available and a definitive diagnosis is established. Which drugs to choose in various situations may be dictated by the interpretation of the results of scientific investigations, but is often also heavily influenced by the views of persons considered authorities, or dictated by local tradition and guidelines. The assumed superiority of one drug above all others in the treatment of various causes of circulatory failure often rests on animal experiments or small single-center studies. Patients with severe circulatory dysfunction and failure are a heterogeneous group, even if enrollment of many hundreds or thousands of patients could give definitive answers about the superiority of one drug above others in circulatory unstable patients *in general*, the conclusions would probably not be valid for all types of patients in all types of situations.

Vasopressors and/or positive inotropes.

A state of acute circulatory failure is most often caused by ***i)*** sub-optimal LV filling, ***ii)*** ischemic reduction of myocardial contractility, and/or ***iii)*** mechanical factors (Part 3-3). Drug overdoses, intoxications, etc. may also precipitate cardiovascular failure through various mechanisms. The choice of agent should be determined by the etiology of the circulatory failure.

Vasopressors in pathological vasodilation.

Loss of vascular tone may be due to ***i)*** partial or total blockage of the normal sympathetic nervous activity, ***ii)*** overproduction/release of endogenous vasodilating agents, ***iii)*** general reduction of vascular reactivity, also called "vasoplegia" or ***iv)*** drugs and toxic agents. The resulting reduction in ABP is due to a combination of *reduced venous return*, leading to reduced stroke volumes, and *low arterial resistance* (see below). In such conditions, the administration of agents that cause smooth vascular muscle contraction has dual effects:

- Contraction of dilated veins increase the venous return, augmenting RV and LV preload, stroke volumes, and C.O.
- Contraction of arterial resistance vessels increases the mean tissue perfusion pressure.

Most such agents are administered i.v., as bolus doses or continuous infusions; adrenaline (epinephrine) is the only such drug that has been proven suitable also for subcutaneous and intramuscular administration. The effectiveness of non-iv administration depends, however, on the local perfusion conditions. In addition, adrenaline *can* also be administered via the airways (see below).

Vasopressors in common use can roughly be divided into

- **Vasopressors that also increase myocardial contractility.**
  - **Catecholamines** like noradrenaline (norepinephrine), adrenaline (epinephrine), and dopamine act directly on α_1 receptors. They also stimulate cardiac β receptors, with inotropic and chronotropic effects; catecholamines are logical choices if vasodilation is accompanied by a reduction in myocardial contractility (e.g. sepsis).
  - **Other agents** that activate catecholamine receptors directly *and* induce a release of noradrenaline from peripheral nerves (e.g. ephedrine).
- **Vasopressors with weak, no, or negative effects on myocardial contractility.**
  - **Pure alpha 1 (α_1) agonists**, e.g. phenylephrine, metaraminol.
  - **Vasopressin.**

See Table 3-2 for dosage and administration.
In addition,

- Angiotensin II agonists.
- NO effect inhibitors like NO synthase blockers or Methylene blue.
- Beta 2 (β_2) receptor inhibitors.

also act as vasopressors but are not first-line agents.

Vasopressor use.

The indication for i.v. infusions or injections (i.e. bolus doses, also called "push" doses) of vasopressors in the treatment of arterial hypotension rest on the assumption that a loss of normal vascular tone has caused

- Venous dilatation, and thus decreased venous return and reduced RV filling volume
- Reduced arteriolar resistance, and thus a decreased tissue perfusion pressure.

As both effects commonly are present simultaneously, the combined effect of reduced C.O. and low arterial resistance may lead to insufficient tissue perfusion pressure and O_2 delivery.

The use of vasopressors to increase the ABP in *hypovolemic* patients, where the vascular beds are already contracted by endogenous adrenergic mechanisms, is not a pathophysiologically valid indication. An exception is their use for very short periods (a few minutes) until sufficient amounts of fluids/blood products can be administered. While the ABP increase after administration of such

agents may sustain the O_2 supply to organs with well-developed autoregulation (e.g. myocardium, brain), it aggravates the hypoperfusion of other vascular beds. In such settings, vasopressor treatment may establish a relatively normal ABP that can mask an insufficient replacement of the blood volume and continuing tissue hypoperfusion. The use of vasopressors in circulatory failure caused by poor venous return should be continuously evaluated and terminated as soon as possible when adequate amounts of fluids have been infused.

In ongoing hemorrhage, increased intravascular pressure may also wash away clots and increase bleeding. The use of vasopressors in such situations should be considered only as a short-term, last-resort intervention until definitive treatment is established. Increasing the resistance to LV ejection may also aggravate cardiac failure in cardiogenic shock.

Most of the commonly used vasopressors exert their vasopressor effect by stimulating vascular α_1 receptors. Metaraminol, an agent frequently used in the 1950-ties to uphold ABP in cardiac shock patients, is now seldom used. In rare instances, however, it may be able to increase ABP when other vasopressors have failed (256).

Vasopressin and its analogs, *NO synthetase inhibitors*, and *methylene blue* are pure vasopressors. In most situations where vasopressor support is urgently needed, an additional inotropic effect is beneficial from an O_2 supply point of view. If, on the other hand, the cause of circulatory failure is cardiac ischemia or pulmonary vascular hypertension, both α_1 (coronary vasoconstriction) and β_1 (increased cardiac $\dot{V}O_2$) receptor stimulation may aggravate the situation. As vasopressin does not contract pulmonary vessels (307), it may be advantageous in cardiac failure secondary to RV failure induced by high pulmonary arterial pressures (308).

Agents that increase the myocardial contractility – Positive Inotropic agents.

When reduced myocardial contractility is the major cause of circulatory failure, administration of agents that increase contractility may be necessary to maintain or re-establish an adequate C.O. Such interventions can increase the SV and decrease the risk of generalized hypoxia as a consequence of low C.O. (see below for details). They are therefore useful in the acute phase of severe systolic cardiac failure (309, 310); long-term treatment does not, however, improve the prognosis in *chronic* heart failure (311, 312, 313, 314).

Agents that stimulate the cardiomyocytes to increase their contractile force differ in their effect on the arterial smooth muscle, and thus in the systemic vascular resistance. As of today (2023), there are three groups of positive inotropic agents in clinical use.

Catecholamines and sympathomimetics increase myocardial contractility through stimulation of myocardial β_1 and β_2 receptors. Their activation increases the intracellular concentration of cyclic adenosine monophosphate (cAMP), which increases the activity of protein kinase A (PKA), which again leads to increased Ca^{++} influx and increased binding of Ca^{++} to the troponin-myosin complex. Negative effects are that the increase in contractile force is associated with increases in heart rate and myocardial O_2 consumption; all such agents also have pro-arrhythmic properties. If major parts of the myocardium are unable to contract (*hypokinetic* or *akinetic* areas, *aneurysmal* enlargement of ventricles), an increase in the contractility of the residual myocardium produces little increase in stroke volume. High levels of catecholamines tend to down-regulate the β-receptors, i.e. a given concentration of catecholamines will generate a weaker response (315, 316, 317).

Some of the catecholamines – *adrenaline* and *dopamine* – may cause vasodilation in low doses due to their simultaneous vasodilating effect mediated by β_2 and DA receptors, respectively, but vasoconstriction predominates at higher doses. *Dobutamine* and *isoprenaline* act as vasodilators regardless of dose levels.

Norepinephrine (NA or Norepinephrine) is a vasopressor also in low doses; it also has inotropic properties but is not as potent in this regard as the other catecholamines. In persons with normal vascular response to α_1 receptor activation, the increase in vascular resistance, and thus in cardiac workload, may partly inhibit the C.O. increase.

Larger doses than those shown in table 3-2 are sometimes employed; substantially higher doses are sometimes necessary to maintain an acceptable perfusion pressure. The incidence of unwanted effects, like tachycardia and arrhythmias, escalate with increasing doses. Since the sympathetic nervous system often already is over-activated, the patient may already be tachycardic. Additional β-adrenergic stimulation may exacerbate the tachycardia (and thereby reduce the diastolic perfusion of the heart), and generate arrhythmias (e.g. rapid atrial fibrillation) that *reduce* the pumping capacity of the heart. Whether those side effects increase mortality *per se,* or whether the need for prolonged infusions of high concentrations of adrenaline/noradrenaline indicate a more grave derangement of cardiovascular function and thus have a poor prognosis, is difficult to ascertain. In this author's experience, patients in septic shock seldom survive if they are unable to maintain an acceptable ABP despite noradrenaline infusions in doses of 0.5-0.7 µg/kg/min or higher, when this agent is used as a single pressor.

Phosphodiesterase inhibitors (e.g. milrinone) exert their effect by inhibiting the intracellular breakdown of cAMP and are thus independent of whether or not the beta-receptors are down-regulated. They also act as vasodilators; the magnitude of this effect on the ABP is difficult to predict and the patients often require simultaneous administration of vasopressors (often infusions of noradrenaline) titrated to maintain an adequate ABP.

Ca^{++} sensitizers (e.g. levosimendan) act by *enhancing* the Ca^{++} binding to the troponin-myosin complex. The increase in contractility comes with a smaller increase in O_2 consumption than the other two types of agents, the accompanying vasodilation may, as for the phosphodiesterase inhibitors, require simultaneous vasopressor administration.

The latter two types of agents are often called *inodilators*, as part of their beneficial effect resides in the reduced vascular resistance to LV ejection. The consequences of such dilatation for the coronary perfusion pressure can be difficult to predict, especially in patients where a pre-existing CHF has induced a chronic state of vasoconstriction.

When cardiac ischemia is the cause of contractility impairment, the increased $\dot{V}O_2$ induced by strong catecholamine stimulation may worsen the already fragile balance between O_2 supply and consumption in borderline areas, and *extend the infarcted area*. Their use must then be kept to a minimum, and care must be taken to avoid unnecessary strain on the heart by increasing the ABP above levels necessary to ensure tissue perfusion. If the contractility is reduced by other factors than ongoing ischemia (e.g. post-ischemia, infections, drugs, toxins, etc.) the dangers of increasing the cardiac O_2 consumption are much smaller.

In animal experiments, α_1-adrenergic stimulation can also increase the contractility of the heart with less risk of tachycardia. This can also be shown for human cardiomyocytes; the importance

of this mechanism is less clear, but the role of α_1 receptors in the heart may become more important as the β receptors are down-regulated in the failing heart (reviewed in ref. 318).

Vasodilators: Nitrites, Cyanides, Alpha$_1$ blockers and others.

By far the most common use of vasodilators is to ameliorate arterial hypertension, which benefits the cardiac function and reduces the risk of cerebrovascular bleeding as well. They are also used for acute reduction of ABP in extreme hypertension (e.g. pheochromocytoma).

In acute *systolic* cardiac failure, reducing the resistance against ejection (i.e. the systolic pressure in the aorta in patients *without* outflow obstruction) increases the stroke volume and reduces the O_2 consumption of the heart (Part 3-1, fig 3-12). The accompanying reduction in diastolic ABP, which may decrease coronary perfusion pressure and flow, is offset by the reduced LV workload and O_2 myocardial consumption. In predominantly *diastolic* LV failure, the benefits of reducing systemic vascular resistance are questionable.

In patients with a *fixed increase* in outflow resistance (aortic stenosis, subvalvular stenosis), a reduction in ABP does not reduce the LV afterload and the O_2 consumption of the heart. In such patients, vasodilation and reduced diastolic pressure may instead precipitate increased myocardial ischemia.

The danger of reductions in coronary perfusion pressure limits to the use of vasodilators in circulatory failure. If the coronary circulation is normal, a diastolic pressure of 40-60 mmHg is assumed to maintain adequate myocardial perfusion (319). The coronary perfusion pressure depends, however, not only on the diastolic ABP but also on the pressure in the right atrium (which is similar to the CVP, see also above); the presence of stenotic parts in the coronary arteries makes the autoregulation mechanism less efficient.

Vasodilators suitable for use in acute conditions (see table 4-2) when titrating local or systemic vascular resistances in circulatory unstable patients is the goal, can be classified as

- **Nitrovasodilators,** which exert their effect by increasing the concentration of nitrogen monoxide (NO) in the vascular smooth muscle cells, which in turn increases the production of cyclic guanosine monophosphate (cGMP) and relaxes the muscle cells. Their half-life is short and the effect rapidly disappears when the infusion is discontinued. They are therefore often the first choice in unstable patients where the tolerance to vasodilation may be difficult to estimate beforehand.
  - *Na-nitroprusside* is broken down to NO and cyanide in the erythrocytes, it is a potent vasodilator in most patients but some are relatively resistant to its effect. It is very short-acting (seconds) and administered as a continuous infusion, high doses may be toxic due to cyanide accumulation.
  - *Nitroglycerine* acts as a donor of NO, it is an effective dilatator of the coronary vasculature and it's action is assumed to be stronger on the venous than the arterial side of the circulation.
- **Alpha-1 (α_1) receptor blockers**. Some of these agents (e.g. phentolamine, dibenzylin) are potent vasodilators with prolonged effect; others, where α_1 blockade is a side effect (e.g. droperidol, chlorpromazine) are less potent. Their half-life is much longer than that of nitrates and should therefore not routinely be used as first-line agents in acute situations. Under austere conditions where controlled infusions of nitrates are not feasible, they can be administered as small bolus doses and titrated after effect as an alternative to nitrate infusions.

The danger of severe hypotension in patients with a high degree of vasocontraction and a low blood volume should be carefully evaluated before such use.

- **Ca^{++} blockers (e.g. amlodipine, nifedipine)** are relatively weak vasodilators. They are usually not the first choice in acute situations but are often used in ICU patients who need long-term vasodilation.
- **Beta-2 (β_2) receptor agonists** (e.g. low dose adrenaline, dobutamine, isoprenaline). These agents are not used primarily for their vasodilation properties; for dobutamine, however, its vasodilating properties are a desired effect in many patients with acute systolic cardiac failure. In patients where its inotropic effect results in a substantial C.O. increase, there may be no

DRUG	SVR	INO	Iv bolus *or* loading dose	Infusion
VASOPRESSORS				
Noradrenaline	⇑⇑⇑	⇑⇑	4-16 µg	0.05-0.5 µg/kg/min.
Adrenaline	⇑⇑⇑	⇑⇑⇑	5-15 µg (*im, sc. 0.3-0.5 mg*)	0.02-0.3 µg/kg/min
Dopamine	⇑⇑	⇑⇑	No Rec	2-15 µg/kg/min
Ephedrine	⇑	⇑	5-10 mg	No Rec
Phenylephrine	⇑⇑⇑	0	50-200 µg	0.5-3 µg/kg/min
Metaraminol	⇑⇑⇑	0	0.2-2 mg.	0.5-1 µg/kg/min
Vasopressin	⇑⇑⇑	0	0.5-2 units	0.01-0.03 units/min
Methylene blue	⇑⇑⇑	0	1-2 mg, 10-60 min ⇒	0.25-2 mg/kg/min.
INOTROPES				
Dobutamine	⇓⇓	⇑⇑	No Rec	2-15 µg/kg/min
Adrenaline	⇑⇑⇑	⇑⇑⇑	As above	
Milrinone	⇓⇓⇓	⇑⇑	20-50 µg/kg, 10 min ⇒	0.2-0.75 µg/kg/min
Levosimendan	⇓⇓⇓	⇑⇑	12 µg/kg, 10 min ⇒	0.05-0.2 µg/kg/min
VASODILATORS				
Na Nitroprussid	⇓⇓⇓	0	No Rec	0.3-3 µg/kg/min
Glyceryl nitrate	⇓⇓	0	No Rec	0.5-3 µg/kg/min
Clonidine	⇓	0	0.5-1 µg/kg, 15 min ⇒	1-4 µg/kg/min
Phentolamine	⇓⇓	0	2-5 mg	No Rec
Chlorpromazine	⇓⇓	0	1.25-2.5 mg.	No Rec
BRADYCARDIA				
Atropine *	0	0	0.4-0.8 mg, max 3 mg	No Rec
Isoprenaline#	⇓⇓⇓	⇑⇑⇑	No Rec	0.01-0.2 µg/kg/min
TACHYCARDIA				
Esmolol	0	⇓⇓	0.25 mg/kg	50-150 µg/kg/min
Verapamil	⇓	⇓	5-10 mg, max 20 mg	No Rec
* Atropine in Organophosphate Intox			*2 mg every 5 min until effect*	*up to 500 µg/kg/min*

#Other catecholamines may be equally effective.

Adrenergic agonists | Loading dose

Table 3-2. *Some commonly used cardiovascular drugs and suggested doses. The effects may vary considerably between individual patients; adjustment of dosage in accordance with the urgency of the situation and the effects observed in each particular patient may be necessary.* **SVR***-effect on systemic vascular resistance,* **INO***-effect on myocardial inotropic state,* **No Rec***-no recommendation.*

decrease in ABP as the increased C.O. compensates for the vasodilation (Part 3-1). Isoprenaline is also a powerful vasodilator but is not used as such due to its chronotropic and arrhythmogenic properties.

- **Angiotensin-converting enzyme inhibitors** and **Angiotensin II receptor blockers** are almost exclusively used for the long-term control of hypertension.
- **Phosphodiesterase inhibitors and Ca^{++} sensitizers – see above.**
- **Alpha-2 (α_2) receptor agonists** (e.g. clonidine, dexmedetomidine) act through central nervous mechanisms. They are not routinely used in acute circulatory failure; dexmedetomidine may be used for sedation during procedures and in the ICU.

Use of vasodilators to reduce SVR or preload.

General vasodilation does not merely reduce the vascular resistance in the systemic circuit. The vessels in the venous system are also dilated, which may reduce the venous return. The preload can then be reduced to sub-optimal levels, it may sometimes be necessary to give intravenous fluids to restore an optimal end-diastolic volume.

Special considerations in the treatment of acute cardiac failure.

The effect of supportive interventions depends on the etiological mechanism.

- Pump failure primarily due to **high vascular resistance** is relatively easy to treat with vasodilators. In patients with a contracted vascular bed, the blood volume may be reduced; initial dosage should start at low levels to avoid a sudden reduction of LV filling volume.
- Pump failure primarily due to **failure of myocardial contractility** usually responds positively to a combination of optimizing the preload, inotropes, and vasodilation.
- Severe **diastolic dysfunction,** even when myocardial contractility is well preserved, is difficult or sometimes impossible to treat successfully.

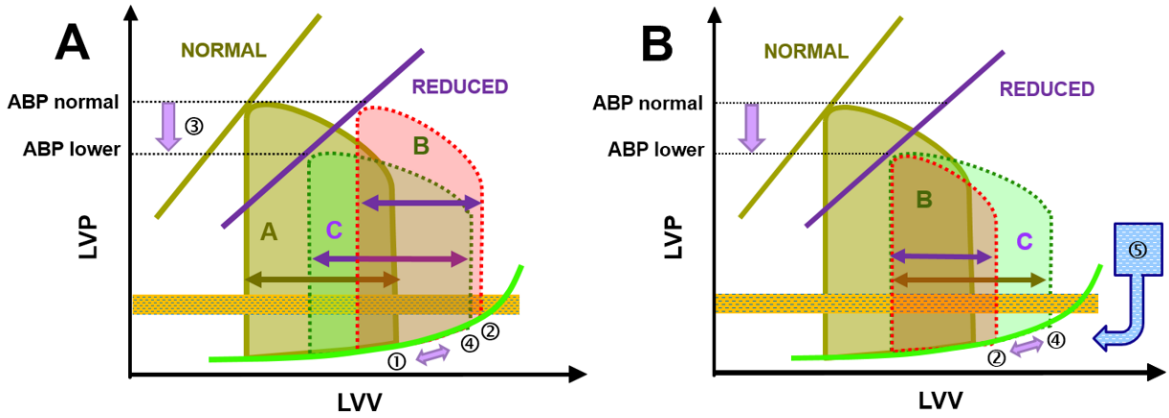

Figure 3-35. *Effect of vasodilators in systolic LV failure, illustrated by changes in the pressure-volume loop (se also fig 4-4) relative to normal state* (**loop A**)**.** *Horizontal arrows indicate the SV, horizontal yellow line indicate the LVEDP where pulmonary edema may occur.* ***Panel A:*** *In hearts with reduced contractility (lilac line), increasing the LVEDV from normal ① to where pressures are close to those precipitating pulmonary edema (yellow broad line) ② can maintain a relatively normal ABP but with a reduced SV* (**loop B**)*. Reducing the resistance to LV ejection by dilating the arterial vasculature and lowering the ABP ③* (**loop C**) *increase the SV and also reduce the LVEDP ④ .*
Panel B: *Dilatation of the venous vascular bed may lead to sub-optimal preload ②* (loop B)*, infusions of fluid ⑤ may then be necessary to optimize preload (loop C) and increase the SV.*

- Myocardial depression caused by **drug overdose, septic shock, or exogenous toxins** may be extremely difficult to treat; supportive treatment sometimes fails and extracorporeal circulation support may be the only way to maintain the necessary flow to vital organs until the drug effects in myocardial function wanes. Although afterload reduction may be beneficial for the heart *per se*, drug-induced reduction of systemic vascular resistance in patients with very low blood pressure is difficult. Such therapy will lead to a further drop in blood pressure, with may endanger the perfusion pressure and blood supply of vital organs. Drugs that reduce vascular resistance (see above) must therefore be administered in small increments and with great care to such patients (see also fig. 3-35).

Special considerations in shock due to vasodilation.

When the primary circulatory problem is **low blood pressure caused by general vasodilation** (e.g. *septic shock*, *spinal shock*, *anaphylactic shock,* or administration of *overdoses of vasodilator drugs*), the low vascular resistance in the arterial system (in some patients reduced to less than 20% of the normal value, as observed by the author) makes it easier for the heart to eject its stroke volume. If the end-diastolic filling volumes are maintained (see fig. 3-29, panel B), the SV, and therefore the C.O. and blood flow to the organs of the body increases.

Although fluid infusions may restore satisfactory diastolic filling volume and therefore heart function, the blood pressure will often continue to be low even though the blood flow to the body is high. When the DO_2 is already satisfactory, further administration of fluids confers no benefits but only increases edema formation. If the blood pressure is insufficient for renal filtration *or* for obtaining an adequate cerebral perfusion pressure, injections or infusion of vasoconstricting drugs (e.g. α_1-stimulating agents, vasopressin) is the only option that will raise arterial pressure to the desired level. A common strategy often utilized in the treatment of such patients is an infusion of noradrenaline; as increasing the resistance may reduce the SV of hearts with a reduced contractility, simultaneous use of drugs with a potent β-stimulating effect (adrenaline, dobutamine) should also be considered.

Treatment of severe bradycardia or tachycardia.

In *severe bradycardia*, atropine or related drugs are often the first choice, since a vagus nerve effect on the conduction system of the heart is the most common cause. If atropine produces little or no effect, drugs with a strong β-adrenergic effect (isoprenaline/dopamine, or small intravenous doses of adrenaline) can be given. In severe bradycardia that requires treatment but responds poorly to drugs, a temporary (or permanent) pacemaker must be considered.

Tachyarrhythmias (except for ventricular tachycardia, which may also lead to ventricular fibrillation) are seldom a cause acute circulatory failure alone, but may contribute to increasing failure if left untreated. Beta-blockers usually reduce the cardiac rate but also reduce myocardial contractility; Ca^{++} blockers also reduce contractility, but to a lesser degree. Other drugs may be preferable in patients with tachycardia and acute cardiac failure.

Mechanical devices for circulatory support.

If conventional treatment fails to stabilize the patient, mechanical interventions like the intra-aortic balloon pump (**IABP**) and extracorporeal membrane oxygenation (**ECMO**) may stabilize the circulation temporarily. The use of such devices is usually limited to specialized hospitals; transport from smaller hospitals to such centers can be effected using portable equipment adapted to use in special ambulances or planes. While enabling the maintenance of a DO_2 that prevents widespread hypoxic organ failure, their availability is limited and the impact on mortality is moderate.

Intra-aortic balloon pump (IABP) consists of a sausage-like inflatable balloon which is an integral part of a catheter inserted (usually through a femoral artery) into the upper part of the thoracic aorta (fig. 3-36). The principle of action is that the balloon (with a volume of about 40 ml, i.e. slightly more than half of a normal stroke volume) inflates at the start of diastole, as soon as the aortic valve closes. This creates a pressure wave that travels retrograde to the closed aortic valve and thus increases the diastolic coronary perfusion pressure. At the beginning of the systole, the balloon is actively collapsed and the pressure in the aorta drops suddenly, which reduces the afterload. While a good way to support a failing heart for a shorter period (stunned hearts), its use *per se* has not been shown to decrease mortality in circulatory failure (320, 321). For IABP to have a favorable effect, the aortic valve must close normally.

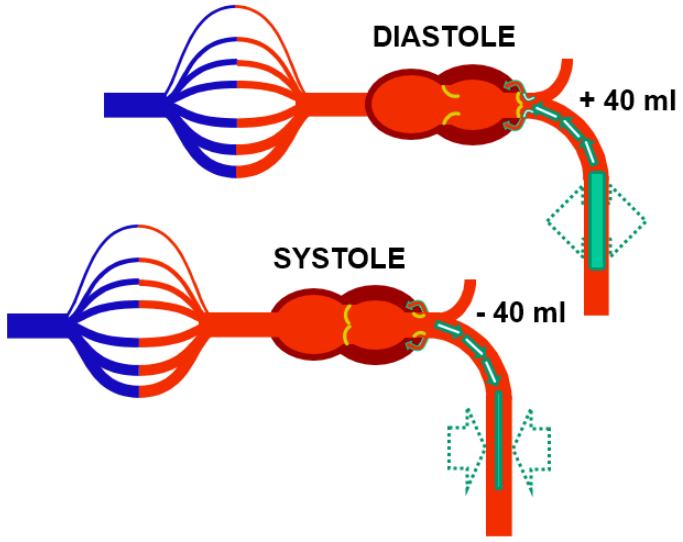

Figure 3-36. *Principle of IABP function: Inflation of the balloon (green) create a diastolic pressure wave that travels retrogradely (green arrows), and increase the coronary perfusion pressure. When the balloon is collapsed during systole, the blood volume in the aorta is reduced. This decreases the force necessary for ejection of the stroke volume.*

Extracorporeal membrane oxygenator (ECMO) consists of an external venous-arterial circuit for the blood, the venous blood drained into the circuit passes by an oxygenator and the oxygenated blood is pumped back into the aorta (fig. 3-37). This principle has been used during heart surgery for many decades; the development of better equipment has reduced the incidence of complications previously associated with long-term use and also reduced the need for anticoagulation. Such treatment is today much easier to organize and use. The circuits used in ICUs are often called extracorporeal life support, **ECLS.** Its use requires cannulation of a major vein for drainage into the circuit, and a major artery for infusion of the oxygenated blood. The output of the circuit pump is limited by the efficiency of the venous drainage.

Both the above methods are resource-intensive and are generally not available in non-specialist hospitals. They may support the circulation, lessen the risk of multiorgan failure, and keep the

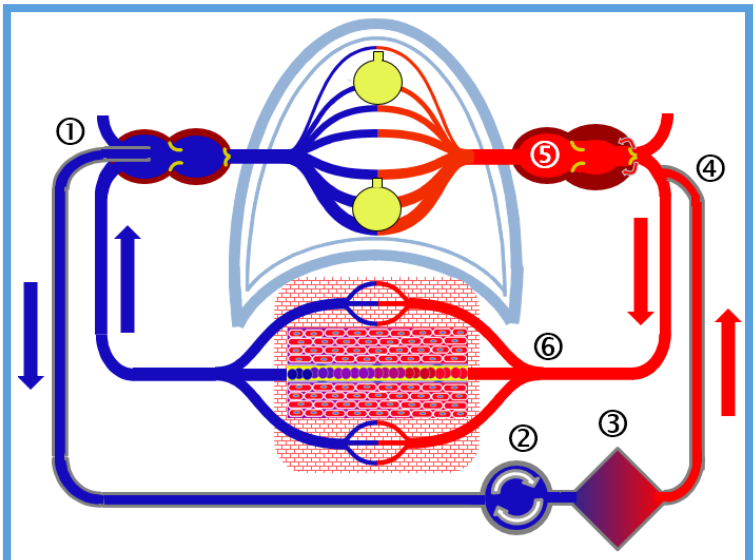

Figure 3-37. *Extracorporeal life support for cardiac failure. Part of the returning venous blood is drained from the right atrium ① and pumped ② through a membrane oxygenator ③ before entering the aorta ④, where it mixes with the part of the blood that pass through the lungs ⑤.*
If half of the returning blood is drained into the external circuit, and the heart is able to pump half of its normal C.O., the total flow remains normal. If the lungs are also affected, the blood draining the lungs ⑤ may be hypoxemic – as illustrated in Part 4, fig 4-46.

patient alive until definitive treatment (e.g. thrombolysis, stenting, transplantation) of the underlying cause can be organized. Both their cost-effectiveness and their effect on long-term mortality have, however, been questioned (322, 323, 324, 325).

Left ventricle assist devices (LVAD) are artificial mechanical hearts of various types that can assist or replace the function of the patient's own heart; the veno-arterial circuit tubing, or the whole device, is surgically implanted and the patient can be mobile. They are not considered a treatment for acute circulatory failure; their main advantage is that the patient is mobile while waiting for a possible cardiac transplant. They need, however, a continuous source of power from external batteries to operate. Due to the complications involved (326) and the huge amount of money and resources required for such treatment (327), it can be offered only to selected patients.

Special catheters that suck blood out from the left ventricle and propel it into the aorta (e.g. Impella® etc.) reduce the force necessary for systolic ejection while ensuring delivery of adequate amounts of O_2 to the tissues. They can be placed percutaneously to avoid severe cardiac failure and cardiogenic shock in selected patients until the heart regains an acceptable pumping capacity or other interventions can replace the failed heart.

Specific interventions.

If the circulatory failure is due to acute vascular incidents like localized *coronary artery occlusion* or *acute pulmonary embolism*, these can be reversed, fully or in part, by successful radiological (Percutaneous Coronary Intervention – PCI) or surgical interventions. Intravenous infusion of thrombolytic agents, although less efficient (328), represents an alternative if the option of invasive interventions is not available during the initial phase of shock. Acute valvular damage and traumatic damage to the heart may require immediate surgical or intravascular interventions. Cardiac tamponade and positive pressure pneumothorax can be rapidly drained with a spectacular improvement in circulation. In *hemorrhagic shock*, reducing or stopping the bleeding is a *sine qua non* for successful therapy. To be successful, such interventions must be carried out within a few hours of the incident (see the Golden Hour concept above), supportive measures (see below) are important until specific interventions can be organized, but must not delay their implementation.

HAEMODYNAMIC MONITORING

Many of the basic diagnostic tools used in evaluations and diagnosis of circulatory shock (see above) are also used intermittently or continuously at the bedside. Not only do they obtain information necessary to establish or confirm a diagnosis, but they also monitor the circulatory response to drugs and other therapeutic interventions and give an early warning of changes in the circulatory state. The response to therapeutic interventions may also create a basis for further therapeutic strategies and prognosis.

The extent and sophistication of circulatory monitoring should be determined by the severity of the circulatory failure, or the perceived risk of the development of such failure, in the individual patient. While the escalation of the monitoring is a continuum, the monitoring regimes can, for simplicity, be grouped into

- Basic non-invasive monitoring (e.g. post-operative or stable cardiac patients).
- Basic invasive monitoring during major surgery and in most ICU patients.
- Advanced circulatory monitoring in circulatory failure and shock.
- Monitoring with a focus on the circulation of special organs (e.g. the brain).

Monitoring of the blood oxygenation, CO_2 content, and acid-base state is not strictly part of hemodynamic monitoring (see Part 4-4 and Part 5-4). They represent, however, an integrated part of the whole picture of circulatory and oxygenation failure; especially the a-v differences in O_2 and CO_2 content of the blood (see above) add valuable information about the state of the circulation relative to the needs of the tissues.

Requirements for clinical benefits of monitoring regimes.

Regardless of extent and sophistication of monitoring regimes, a patient benefit can only be expected when the personnel responsible for patient care at the bedside are able to interpret the measured and calculated parameters correctly, are familiar with the limitations of the methods employed *and* know what to do in response to expected as well as unexpected changes. Alterations with ambiguous implications must be supplemented by further investigational methods when necessary.

The chosen parameters should

- Contribute to resolving uncertainties as to the circulatory state.
- Give early warnings about changes in the cardiovascular state.
- Induce appropriate pre-defined interventions or changes in therapeutic strategy when they deviate outside pre-set limits.

In addition, there must be a clear understanding of which changes in the parameters that constitute a *positive response* to therapeutic adjustments.

Monitoring in acute and sub-acute phases of circulatory failure.

In situations where rapid changes can be expected to occur (e.g. intraoperatively and initial postoperative phase, in prehospital settings, on arrival in the emergency room or an ICU), the impact of measured and calculated parameters on clinical decisions and therapeutic interventions is large. In addition, the response to the initial therapeutic interventions may support or negate the first assumptions about the etiology of the failure.

In *stabilized* ICU patients, the cause of failure is usually determined and organ dysfunction or damage may already established. Monitoring during this phase still offers valuable information about the progression of the disease and the need for further interventions; due to the hetero-

geneous nature of ICU populations, however, the impact of information from monitoring regimes on morbidity is difficult to prove.

Monitoring regimes can, somewhat arbitrarily, be classified into three stages:

Basic non-invasive bedside monitoring consists of continuous recording of

- Heart rhythm from continuous EKG monitoring (arrhythmias may signal myocardial ischemia or reperfusion, tachycardia may signal hypovolemia). An increasing frequency of aberrant ventricular rhythms is a danger signal.
- ABP (increases may signal pain or other causes of sympathetic discharge, decreases may indicate bleeding or other processes that affect cardiac- or vascular function).
- SpO_2 (falling values may signal hypoventilation or reduction in pulmonary gas exchange function, as in alveolar edema, aspiration to the airways, pulmonary emboli, etc.).

In basic invasive monitoring, measurement of heart rhythm and SpO_2 as above, plus

- Continuous measured of ABP utilizing an indwelling arterial catheter; arterial blood gases may be drawn from this catheter at appropriate intervals.
- The pressure inside a central intrathoracic vein (CVP is usually representative of the RV end-diastolic pressure) may be measured frequently or continuously. See caveats above concerning interpretations!

In advanced invasive monitoring, additional measurement may consist of

- Cardiac output (using indicator dilution, pulse contour analysis, trans-esophageal Doppler, or ECHO-Doppler techniques).
- Calculation of fluid accumulation in the pulmonary tissue (”lung water” measurements).
- ECHO examinations to estimate changes in correlation between filling pressures and –volumes in the individual patient.
- Intermittent (or continuous) calculation of the a-v O_2 content differences and v-a CO_2 differences, using changes in the S_aO_2-S_vO_2 as a surrogate), sometimes also the v-a PCO_2 difference.
- Intermittent measurements of diastolic filling pressures of the left ventricle (PCWP) and pressures in the pulmonary artery (PAP), using a PA catheter.

Such measurements permit calculations of various hemodynamic parameters and monitor whether the calculated DO_2 is matched to the individual patient’s needs.

Monitoring with a focus on the circulatory state of organs not affected by the global DO_2 of the organism is outside the scope of this compendium. Such devices include the monitoring the intracranial pressure (which indicates the transmural perfusion pressure in cerebral edema and intracranial bleeding) and the blood flow in intracerebral vessels, the state of the microcirculation on various organ surfaces, and parameters indicating early tissue hypoxia by measuring lactate in tissue fluid (e.g. microdialysis technique).

Under austere conditions, monitoring may be limited to observing cerebral function, skin color and temperature, and palpation of the arterial pulse. Under such circumstances, the number of therapeutic options available will probably also be severely limited. Maintaining free airways and performing basic cardiopulmonary resuscitation in pulseless persons, however, do not require any equipment, only basic skills. Equipment for administration of supplemental O_2 and assisted manual ventilation plus for i.v. infusions of crystalloid fluids and bolus injections of adrenaline are often available even under austere conditions, and may stave off tissue hypoxia until equipment for more advanced treatment becomes available.

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PART 4. LUNG FUNCTION, DYSFUNCTION, AND FAILURE

4-1. NORMAL LUNG FUNCTION AND OXYGENATION OF THE VENOUS BLOOD
4-2. HYPOXEMIA, HYPERCARBIA, AND ALVEOLAR VENTILATION IN NORMAL AND DYSFUNCTIONAL LUNGS
4-3. RESPIRATORY FAILURE AND THE O_2 CONTENT OF THE BLOOD
4-4. TREATMENT OF HYPOXEMIA AND HYPERCARBIA, MONITORING

INTRODUCTION.

The **major tasks** of the human lungs are:

- **To replenish the venous blood with O_2 in amounts at least equal to that consumed by the tissues *and* to optimize the PO_2 of arterial blood relative to that in the alveolar gas.**

To achieve complete re-oxygenation of the venous blood,

i) Almost all the blood traversing the lungs must pass alveoli filled with gas containing a sufficient amount of O_2, and equilibrate with the alveolar gas before leaving the lungs.

ii) The amount of fresh O_2 supplied to the alveolar gas during each inspiration must match the amount of O_2 consumed during the ventilation cycle. To accomplish this, the ventilation volumes must adjust continuously in proportion to changes in the O_2 consumption of the organism ($\dot{V}O_2$), (see Part 2-1).

- **To excrete the metabolic end product carbon dioxide (CO_2) at the same rate as its production.**

To achieve this,

i) Most of the venous blood traversing the pulmonary vascular bed must pass alveolar areas where the CO_2 can diffuse into the alveolar gas and subsequently be excreted with the expired gas.

ii) The pulmonary ventilation volumes must adjust continuously to match changes in CO_2 production and to maintain a blood-to-alveoli CO_2 gradient that optimizes diffusion.

As the tissue generation of CO_2 during aerobic metabolism changes in proportion to variations in $\dot{V}O_2$, the change in ventilation relative to variations in $\dot{V}O_2$ also accomplishes the task of adjusting the excretion of CO_2. The equilibrium between CO_2 production and excretion is maintained by healthy lungs during large variations in PCO_2 production.

- **To adjust the excretion of CO_2, and thus the P_aCO_2, to levels where the arterial H^+ level remains close to normal** (pH 7.40), **or at least within the survivable range**.

To achieve this, any change in the arterial blood $[H^+]$ alters the depth and frequency of the ventilation, and thus the excretion of CO_2. This regulation mechanism is *independent of* changes in $\dot{V}O_2$, P_aO_2, and P_aCO_2 (see also Part 5-1).

4-1. NORMAL LUNG FUNCTION AND OXYGENATION OF THE BLOOD

GAS EXCHANGE AND GAS CONDUCTION IN THE LUNGS

The gas-filled spaces of the lungs can be divided into

- **The areas of gas exchange,** i.e. the **alveolar-capillary units**, where the pressure of gases in the pulmonary capillary blood equilibrates with those in the alveoli. In normal lungs, the pressures of O_2, CO_2, and other gases in the capillary blood become equal to the pressures in the alveoli it perfuses before the blood leaves the alveolar areas.
- **The areas of gas conduction**, through which the areas of gas exchange communicate with the ambient air, but where no gas exchange occurs. This is the *anatomical dead space.*

This division is not absolute, some small airways (respiratory bronchioles, alveolar ducts), function as areas for both gas exchange *and* gas conduction. Also, some areas where gas exchange normally takes place may fail to do so if the perfusion pressure becomes too low to ensure flow through the capillaries, creating a **physiological alveolar dead space** that do not participate in the gas exchange (see below for details).

The gas conduction area consists of a system of branching airways where occlusion at any point deprives the airways distal to that point of ventilation; thereafter, no exchange of gas takes place in airways distal to the occlusion (see Part 4-2). There are some collateral connections between peripheral airways (1), but the magnitude, as well as the clinical importance of such *collateral ventilation* for gas exchange in pulmonary diseases, is uncertain.

The alveolar-capillary unit – the areas of gas exchange.

The air sacs, the alveoli, are the smallest gas exchange unit in the lungs. An *alveolus and its perfusing capillaries* constitute the **alveolar-capillary unit.** The number of alveoli in a normal adult lung varies with the lung volume, which again is correlated with the individual's height (2, 3, 4). The mean number of alveoli was previously assumed to be some 300 million (5, 6); newer investigations suggest a substantially higher mean number of 480 million with a considerable individual variation (274-790 million) correlated to the total lung volume (7). The total volume of gas in all the alveoli of a normal lung at the end of a passive expiration (see also functional residual capacity (**FRC**) below) is in the 2-3 liter range, varying with lung size and body position and changed by disease.

Most of the alveolar walls consist of a dense network of capillaries with some supporting tissue (fig. 4-1). The total surface area of all alveoli in a 75 kg person is calculated to be around 130 m^2; the corresponding capillary surface is about 115 m^2 (8). This ratio indicates that around 85-90% of the alveolar surface facing the gas (the thin wall, fig. 4-1) consists of pulmonary capillaries, illustrating the density of the capillary network in alveolar walls and septa.

On the surface facing the alveolar gas, an extremely thin film of cytoplasm belonging to the *type 1 alveolar cells* covers the capillary network. This film covers around 95% of the alveolar surface and represents no obstacle to the diffusion of O_2 and CO_2. The other type of alveolar cells, the *type II alveolar cells*, are more cuboidal and cover the rest of the surface. The type II cells are the ones producing surfactant (see Apx); they can also differentiate into type I cells if these become damaged or destroyed (9).

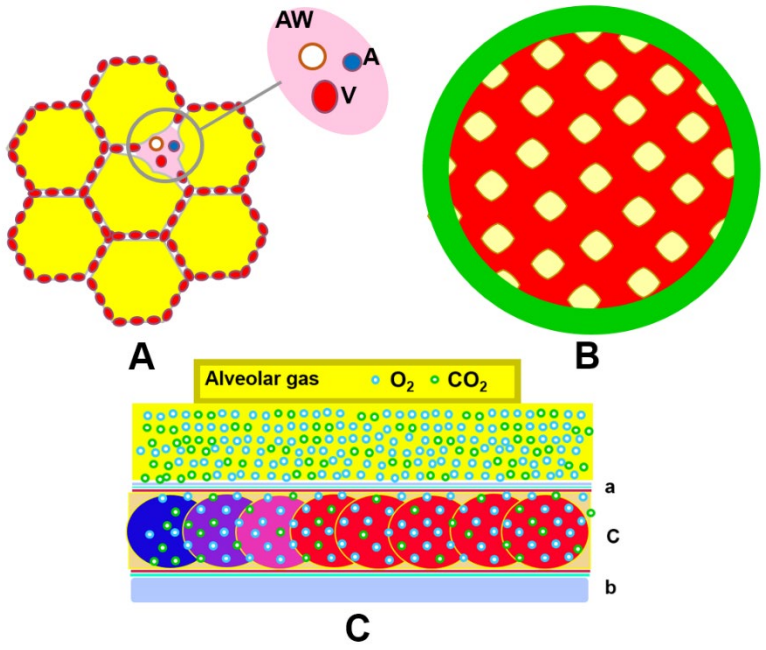

Figure 4-1. **A.** *Schematic view of a group of alveoli, where most of the alveolar wall consists of a network of capillaries (alveolar vessels). Also show (within the oval) is an interstitial space where the small precapillary arterioles* **(A),** *post-capillary veins* **(V)** *and small airways* **(AW)** *run. Generation of hydrostatic oedema starts within these interstitial spaces, enters the small airways and then fill the alveoli.* **B.** *Schematic view of a capillary wall. Very short capillaries form a network so dense that most of the alveolar wall consists of capillaries through which the blood flows like a film or sheet.* **C.** *The interface between alveolar gas and capillary blood consists of a thin wall* **(a)** *that represents no barrier to gas exchange with the blood in the capillary* **(c)***; the thick wall* **(b)** *allows little gas exchange.*

The diffusion distance between alveolar gas and blood is small, the thickness of the thin wall (see fig. 4-1) is only 0.2-0.3 µm and the number of capillaries is great. In normal lungs and with a normal C.O., the PO_2 and PCO_2 in the capillary blood becomes equilibrated with the alveolar gas long before the blood leaves the alveolar-capillary units. When all perfused alveoli are adequately ventilated, the PO_2 in the alveoli and arterial blood are close to equal. Equilibrium occurs even when blood flow rates are close to maximal obtainable levels (see also pulmonary circulation).

In addition to the inspired **tidal volumes** and their **frequency**, the ambient barometric pressure ($\mathbf{P_B}$), the fraction of O_2 in inspired gas ($\mathbf{F_iO_2}$), and the alveolar CO_2 pressure ($\mathbf{P_ACO_2}$) determine the oxygen content of the alveolar gas. When these three factors are known, and no "second gas" is present, the mean alveolar PO_2 ($\mathbf{P_AO_2}$) can be calculated (see alveolar gas equation).

Under extreme conditions (e.g. at high altitudes, where very low alveolar O_2 pressures and low venous SO_2 are combined with high capillary flow rates), *complete* O_2 equilibration between alveoli and capillaries may not always be achieved (10). Within the normal physiological range of blood gases at sea level, however, a change in P_AO_2 and P_ACO_2 in healthy lungs results in a corresponding change of PO_2 and PCO_2 in the pulmonary capillaries, and thus in arterial blood (see hypoxemia with normal lungs below).

Pulmonary acini - the terminal unit for gas exchange.

The alveoli are organized into larger structural units; the **pulmonary acini.** An acinus encompasses a group of alveoli with a common gas supply, a **terminal bronchiole,** it is also perfused by the same **terminal branch of the pulmonary artery** (see below). The capillary blood from each acinus is drained, however, by several veins. The airways within the acini are organized into **respiratory bronchioles**, **alveolar ducts,** and **alveolar sacs** (fig. 4-2) which represent the terminal gas exchange units of the lungs. The adult lung contains some *26 000 to 32 000 acini;* each acinus contains some *10 000 to 20 000 alveoli***.** Under normal conditions, the acinus

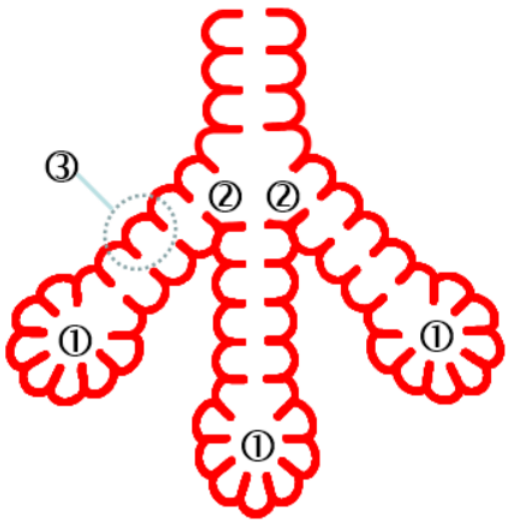

Figure 4-2. *Schematic 2-dimensional depiction of an acinus with alveolar sacs ①, alveolar ducts ②, and alveolar septa ③. A single erythrocyte may pass through the capillaries of several alveoli before entering a vein.*

is the smallest unit for gas exchange that can be identified by methods for measuring the V/Q inhomogeneity of the lungs (11).

The acini are organized in a complicated three-dimensional structure rich in **alveolar septa,** which ensures a maximal surface area for contact between gas and blood (12, 13)**.** Detailed descriptions of lung morphology and its importance for efficient gas exchange can be found in refs 9, 14, 15.

If the supplying terminal bronchiole is occluded, the O_2 within the alveoli is rapidly resorbed by the perfusing blood. When the P_AO_2 becomes equal to that of venous blood, the alveoli within that acinus cease to add O_2 to the passing blood. Focusing on the gas exchange within an acinus is more rational than focusing on individual alveoli; especially the positive effect of increasing the total pulmonary gas volume through increasing the airway pressure (PEEP and CPAP, see Part 4-4) in patients with pulmonary alveolar edema (see Part 4-3) is easier to understand.

Areas of gas conduction and humidification.

Conduction. The alveolar gas communicates with the ambient air outside the body through a system of branching large and small airways. The **upper airways** consist of the *naso-oropharynx* and the *larynx,* with the vocal cords and trachea. The airways **below** (distal to) **the trachea** are **the lower** (or intrapulmonary) **airways**, and may, in order of descending diameters, be grouped into three main classes: ***i)*** **cartilaginous bronchi**, ***ii)*** **bronchioles without cartilage,** and ***iii)*** **terminal bronchioles**. In the conducting parts of the airways, there is no exchange of gas between air and blood; the gas-filled space within the upper and lower conducting airways represents the **anatomical dead space**. The volume of this space varies with body size and is about **150 ml** in a person of normal build (see also below).

Humidification. In addition to the conduction of gas, an important function of the conducting airways is to humidify the inspired gas before it reaches the alveoli. This process is so effective that the alveolar gas is 100% humidified even at very high inspiratory flows, the partial pressure of H_2O vapor in the alveolar gas is always equal to the H_2O vapor pressure at body temperature (6.3 kPa *or* 47 mmHg at 37°C (98.6°F)).

MECHANICAL FORCES THAT ACT ON THE LUNGS

To create a gas flow through the areas of conduction, a pressure difference must exist between the alveolar gas and the ambient air. During spontaneous inspiration, an alveolar pressure lower than that of ambient air is created by contraction of the inspiratory muscles. During a passive, non-forced expiration, the elastic recoil of the lung tissue creates higher pressure in the alveoli than the ambient one, and the gas flows out.

The seal between the lung surface and thoracic cavity.

A thin cellular layer with a smooth surface, the pleura, covers the outer surface of the lungs (the *visceral pleura*) and the inner surface of the thoracic cavity and the diaphragm (the *parietal* or *thoracic pleura*). Between the two blades, there is a thin film of fluid; the capillary force of this fluid (see Apx) effectively seals the blades together (fig. 4-3).

As long as this seal is unbroken, a very strong force is needed to pull the two blades apart in the perpendicular plane; in the parallel plane, however, the two blades slide freely against each other.

Forces favoring expansion of the lung tissue.

The bony structure of the *thoracic cage* is built to expand. Even without any respiratory muscle activity, it will expand by a volume of approximately 500 ml if the seal between the thoracic cage and the lungs is broken, and air can flow freely in (16). Upon activation of the inspiratory muscles, the volume of the thoracic cage increases further; when the thoracic cage expands and the diaphragm contracts, the lungs expand passively as long as the seal between the two pleura blades is intact.

Forces favoring contraction of the lung tissue.

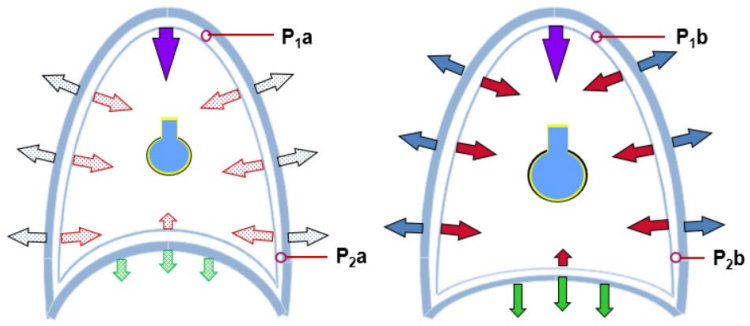

Figure 4-3. *Forces acting on the lungs at end expiration (left) and end inspiration (right). Blue arrows: Expanding forces, Red arrows: Contracting forces. Lilac arrow: Lung weight, Green arrows: Contraction of the diaphragm. Pleural pressures are moderately negative at end expiration (typically* P_1a *= - 8 cm*H_2O *and* P_2a *= 0 cm*H_2O*), decreasing to* P_1b *= -18 cm*H_2O*, and* P_2b *=-10 cm*H_2O*, respectively, after inhalation of a* V_T *of approx. 1000 ml.*

The lung tissue contains **elastic fibers**, running in all directions through the tissue and acting like elastic bands; these fibers are actively trying to make the lung tissue contract. In addition, the inside surface of the alveoli is covered by a thin film of fluid. The **surface tension** generated by this film also favors a contraction of the lung tissue; the presence of *surfactant* attenuates the surface tension effect at low alveolar volumes (see Apx). The combined force of elastic fibers and the surface tension causes the lungs to contract and expel part of the alveolar gas during expiration as a passive process, without the participation of respiratory muscles. If the seal between the pleura blades is broken, the forces favoring contraction of the lung tissue are unopposed; when the lung tissue contracts, the airways collapse and create *atelectasis*.

Mechanical forces and intrapleural pressures in the upright position.

In a sitting or standing position, the lungs may be envisioned as being suspended from the apical part of the thoracic cage, while the basal part rests on the diaphragm. The *specific weight* of the lung tissue is about 0.25-0.3; gravity stretches the upper part of the lung tissue, while the lower part is compressed by the weight of the lung tissue above (fig. 4-3).

The opposition between contracting and expanding forces creates slightly negative pressures between the two pleura blades. At the end of a passive expiration, the mean intrapleural pressure is approximately 5 cmH_2O (3.75 mmHg). When **sitting or standing**, the intrapleural pressure is lowest (i.e. most negative relative to atmospheric pressures) close to the apex and highest (i.e. least negative or approaching zero) where the lung base rests on the diaphragm (fig. 4-3).

Mechanical forces and intrapleural pressures in the supine position.

When **lying supine**, the **weight of the abdominal organs,** which in terms of pressure behaves as a gel-like mass, exert pressure against the underside of the diaphragm and thereby compress the lung tissue. This pressure increases with increased gravity; the pressure forcing the diaphragm upwards and into the thoracic cage is greatest where the mass of abdominal cavity contents above is largest. In the supine position, the pressure against the dorsal part of the diaphragm is, therefore, highest and compresses the lung tissue (fig. 4-4, see also Part 4-3, fig 4-37 and 4-45).

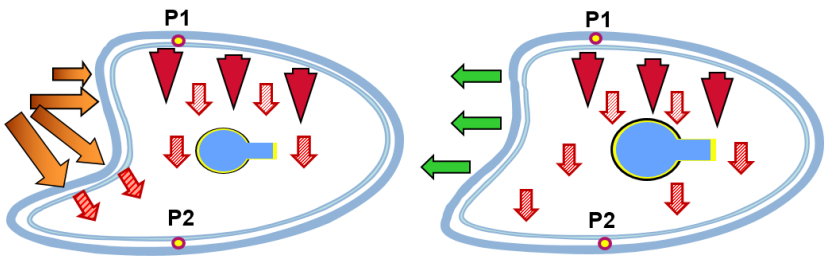

Figure 4-4. *Distribution of inspired gas in the supine position. With a relaxed diaphragm at end expiration (left), the abdominal cavity contents displace the diaphragm further upwards into the thoracic cavity; compression of the lungs is then most pronounced in the dorsal-caudal part. When the diaphragm contracts during inspiration (right), the change in alveolar volume is greatest in this part, which then receives most of the inspired gas. The difference in pleural pressure between the upper (P1) vs the lower (P2) part of the lung is smaller than in the upright position.*

If the general tension of the diaphragm and/or the force of its contraction is reduced, the area of lung tissue located on the other side of this part of the diaphragm will be poorly ventilated and may collapse, creating atelectasis. The impact of the pressure exerted by the abdominal organs, and thus the creation of hypoventilated and atelectatic areas, increases in overweight individuals, in patients with significant edema of intraabdominal organs, and those with large quantities of ascites or gas within distended bowels (see also Part 4-4 for *prone position*).

THE PULMONARY VENTILATION CYCLE

Spontaneous inspiration.

Inspiration. With the contraction of the inspiratory muscles, the walls of the thoracic cage expand and the dome of the diaphragm muscle descends. With an intact seal between the thoracic cage and the lungs, the lung tissue expands passively. The gas pressure within the airspaces in the lower airways decrease, after which ambient air flows into the lungs to equalize the pressure. When the pressures again become equal shortly after the end of inspiration, flow ceases.

The **inspiratory muscles** active during *quiet breathing* are the *diaphragm*, the *external intercostal*, and the *scalene* muscles; during *forced inspiration*, accessory muscles (e.g. sternocleidomastoid, latissimus dorsi muscles, etc.) increase the force of the thoracic cage expansion. Of

clinical importance is that the nervous supply of the diaphragm, which is the single most important inspiratory muscle, stems from the C_3-C_5 segments. The diaphragm may therefore continue to function even if an injury to the thoracic spine paralyzes most of the other respiratory muscles.

The deeper the inspiration, the more the lung tissue is stretched and the more negative the pressure (relative to atmospheric pressure) between the two blades of the pleura. If the expansion of the lung tissue is impeded or prevented as a result of high airway resistance or obstruction of the airways (e.g. bronchospasm, foreign bodies, secretions) or by the lung tissue being stiff and lacking in elasticity (low lung compliance Apx, e.g. pneumonia, ARDS see Part 4-3), a greater muscular effort will be required to expand the lungs. The intrapleural pressure then becomes more negative. Under normal conditions, the work of respiratory muscles represents about 5% of the body's O_2 consumption; during labored breathing, the effort of the respiratory muscles may increase the total O_2 consumption by as much as 30% (17).

Distribution of inspired air during spontaneous ventilation.

(See Part 4-4 for conditions during positive pressure ventilation).

In the upright position. Due to the gravitational forces acting on the lungs, the alveoli situated in the lowest part of the lung are compressed by the weight of the pulmonary tissue above. Before the start of the next inspiration, these alveoli, therefore, contain smaller gas volumes than those situated in the upper part (fig. 4-5). At the end of a deep inspiration, the gas volume in the lower and upper parts of the lung becomes close to equal. When sitting or standing, the gas volume in the lower (i.e. closest to the diaphragm) part of the lung tissue increases more than in the upper part, the alveolar ventilation in the lower part of the lungs is then greater than in the upper part. As the lower part of the lungs are best perfused (see West's model), ventilation and perfusion are well, but not perfectly, matched (see V/Q ratios).

In the supine position. Most patients needing acute pre-hospital or in-hospital emergency care, or being cared for in an ICU, are in the supine position (the *prone* position is increasingly common during treatment of patients with severe ARDS – see Part 4-4 therapy). The same goes for the majority of surgical procedures. When supine, the contents of the abdominal cavity force the relaxed diaphragm upwards; the pressure exerted on the relaxed diaphragm is highest at the dorsal-caudal part of the thoracic cavity (fig. 4-4). Consequently, the alveoli in this part are smallest at end-expiration, and, analogous to the lowest situated alveoli when upright, have the largest change in volume at the end of spontaneous inspiration and thus receive most of the fresh inspired

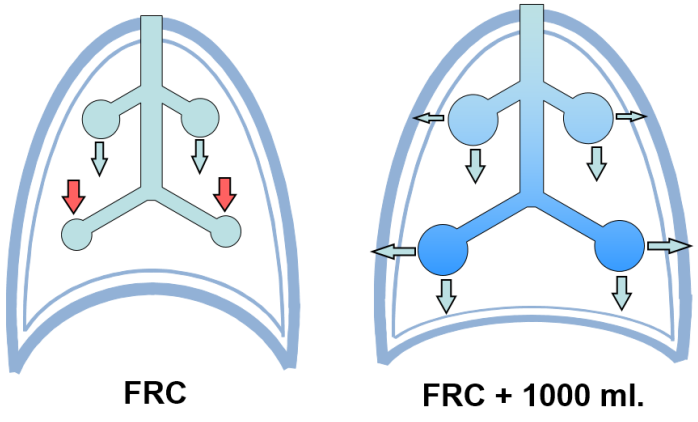

Figure 4-5. *Distribution of the inspired gas in the upright position. Due to the weight of the lung tissue, the lowest situated alveoli have the least mean alveolar volumes before start inspiration (FRC). After a deep inspiration, most alveoli have the same volume, i.e. more of the fresh gas goes to the lower alveoli.*

gas. If the activity of the diaphragm is reduced, leading to low tidal volumes, or absent, as during controlled ventilation, the risk of atelectasis is also highest in this area.

Expiration.

When the inspiratory muscles relax, the force of the elastic properties of the lungs and the alveolar surface tension (see above) causes the thoracic cage to contract again. During quiet breathing, this is a passive process, requiring no use of muscles; expiratory airflow ceases when the intra-alveolar gas pressure becomes equal to the ambient pressure. During forced ventilation (e.g. hyperventilation induced by severe hypoxemia, physical exertion, or metabolic acidosis), increasing the intrathoracic pressures may be necessary to expel increased tidal volumes more rapidly. The muscles most important for forced expiration are the *internal intercostal* and the *abdominal muscles*, but others (e.g. *latissimus dorsi*) may also contribute.

Adjustment of the force exerted by the respiratory muscles; the airway resistance.

The force exerted by the respiratory muscles adjusts to

- The compliance ("stiffness") of the lung tissue.
- The rate of air flow necessary for inspiration and expiration of a tidal volume that can maintain a constant composition of the alveolar gas.
- The total airway resistance to gas flow.

The resistance (**R**) in a system of tubes (blood vessels, airways) depends on the number of parallel tubes and their average diameter (see Apx for calculation of resistance). As the resistance varies with the inverse value of the tube radius (**r**) in the fourth power (r^4), a halving of the airway *radius* (e.g. by upper airway obstruction or bronchospasm) while the other factors remain constant leads to an *airway resistance increase by a factor of x 16*. The pressure gradient between ambient air and alveoli must then increase 16 times to maintain the same airflow as previously. Under normal circumstances, the major part of the airway resistance is located in the upper airways and cartilaginous bronchi. In asthma and other conditions characterized by bronchospasm (Part 4-3), the resistance increases in more or less all airways proximal to the respiratory bronchioles.

Changes in the stiffness and elastic properties of the lung tissue (inflammation, fibrosis, emphysema, and edema) also increase the force necessary to expand the lungs and increase the work of the respiratory muscles.

GAS VOLUMES IN THE LUNGS

In healthy persons, the gas volumes in the lungs during the various phases of the respiratory cycle vary with factors like age**,** weight, sex, ethnicity, build, physical fitness, etc. In persons of relatively normal build, they are first and foremost correlated to the person's height (2, 3, 4). Height is also used to calculate predicted (ideal) body weight, which again is used for calculations of recommended tidal volumes during mechanical ventilation (18),(see Part 4-4).
The volumes of gas also vary with the individual's position; gas volumes measured when sitting are generally larger than those measured in the same individual when supine (see FRC below).

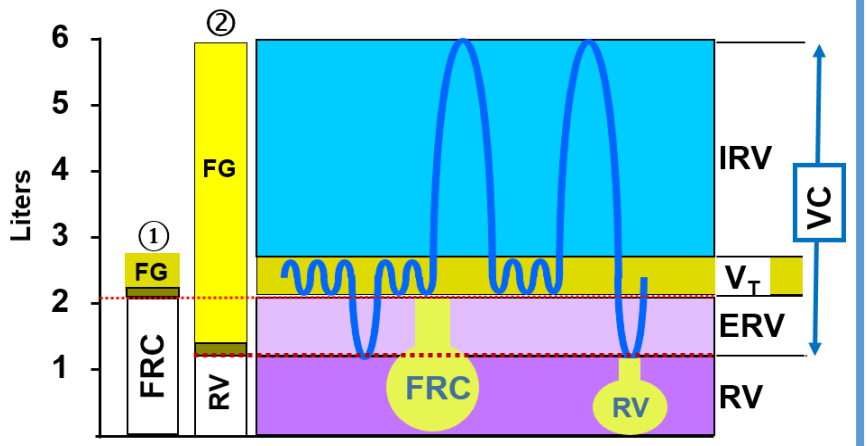

Figure 4-6. *Gas volumes in the lungs (see text).* **V_T***: Tidal volume,* **FRC***: Functional residual capacity, which consists of the residual volume* (**RV**) *and the expiratory reserve volume* (**ERV**). **IRV***: Inspiratory reserve volume,* **VC***: Vital capacity. During normal quiet breathing* ①*, each* V_T *supplies around 15% of fresh gas* (**FG**) *to the FRC. When breathing with maximal* VC ②*, each* V_T *supplies an amount of fresh gas around 3-5 times that of the* RV*.* ▬ *Anatomical dead space.*

The **Total Lung Volume or -Capacity (TLC)** is the volume of gas within the lungs at the end of a maximal inspiration. The mean volume in healthy persons is typically around 4.3 liters (females) to around 5.7 liters (males), with considerable individual variations (19). In patients with emphysema, the TLC may be higher (20), in persons participating in breath-holding competitions, TLCs in the 8-10 liters range has been reported (see below) (21).
The TLC determines the total reserve capacity of O_2 in the alveolar air during *voluntary* breath-holding (e.g. during free diving); the FRC (see below) determines the O_2 reserve capacity during an *involuntary* respiratory arrest, e.g. cardiac arrest, respiratory muscle paralysis, etc. The TLC minus the residual volume (the gas volume remaining after a forced expiration, see below) determines the maximum tidal volume V_T – the Vital Capacity (**VC**), see below and fig. 4-6.

The **anatomical dead space (ADS)** is the part of the airways in which no gas exchange with the blood takes place, it consists of the upper airways, trachea, and bronchioles. It varies with body size, and is related to both ideal weight (approximately 2.2 ml/kg (22)) and height (23). Individual variations are substantial (24) and the volume varies with body position and breathing pattern; the ADS volume is reduced by 40-50% when breathing through an endotracheal or a tracheostomy tube. For convenience, an ADS volume of 150 ml for persons of normal size is used in the calculations of alveolar ventilation below.

The **Functional Residual Capacity (FRC)** of the lungs is the volume of gas left in the lungs at the end of a passive expiration; at this point, there is an equilibrium between the forces trying to contract the lung tissue and those trying to expand the thoracic cavity (see above). This volume is measured utilizing various methods (e.g. Helium dilution, Nitrogen washout, Plethysmography); common to all of them is that the volume measured includes both the *end-expiratory alveolar gas volume* and the *gas in the conducting airways (ADS, see above)* (25).
The calculated ADS must be deducted to estimate the true alveolar gas volume. The volume of gas in the anatomical dead space of a healthy person represents only 5-7% of the total FRC, the error of not correcting for the ADS is therefore small, but increases when the alveolar gas volume decreases. Estimations of the remaining gas volume in the lungs at end-expiration can also be estimated from computer tomography (CT) (26).

The volume of O_2 in the FRC represents the reserve supply of O_2 at the start of a period of apnea in a healthy person (see Pulmonary reserves of O_2 during apnea); the volume of FRC is therefore

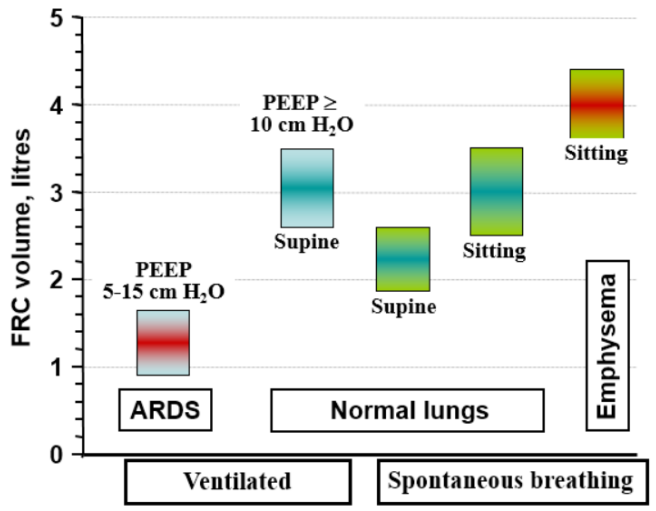

Figure 4-7. *Comparison of ranges of FRC volumes, as measured under various conditions. Volumes shown are based on values given in papers referenced to in the text.*

of great importance in connection with anesthesia, acute- and intensive care. In apnea, and with preserved circulation, the volume and gas composition of the FRC at the point where ventilation ceases determine how fast hypoxemia develops. In apnea due to voluntary breath-holding (see below), the O_2 supply within the alveoli at total lung capacity may be the deciding factor for how long the O_2 content of the arterial can be maintained at levels compatible with aerobic metabolism.

The FRC volume changes with the position of the body and with diseases, applying a positive end-expiratory pressure increases the FRC (see below). As most published FRC measurements are carried out in sitting subjects with normal muscle tone, normal mean values of FRC are often given as approximately 2.5-3 (19) or 3.5 liters (3, 27, 28). In anesthesia, emergency- and intensive care, patients are usually supine, often with reduced or no muscle tone, the same goes for patients who become apneic due to cardiac arrest, etc. In supine, spontaneously breathing healthy persons, the FRC is substantially reduced; mean values of 2.6 l (28), 2.4 l (19), 2.2 l l (29), or 2.1 l (30) has been reported.

Increasing PEEP in ventilated patients by 10 cmH_2O may augment the end-expiratory gas volume by close to 30% (26) or even 50% (31). The gas volumes measured under such circumstances are not representative of the FRC according to the classical definition but do represent an estimate of the volume of the gas-filled alveolar space. The gas volume in the lungs of patients where PEEP is applied is often called the End Expiratory Lung Volume (EELV) (32) to distinguish it from the "true" FRC. In mechanically ventilated patients (see Part 4-4), the mean EELV, even with a PEEP of 5 cmH_2O, was found to be 2.2 l in persons without lung failure, 1.4 l in persons with primary lung failure, and 1.2 l in persons with secondary failure, with an about 30% volume increase when PEEP was increased to 15 cmH_2O (26). Similar data have been reported by others (31, 33); FRC values of less than 1 liter in patients with severe lung failure have also been reported (34). An overview of FRC/EELV measured under various circumstances, based on the references above, is shown in fig. 4-7. FRC values of 2.2 l or 2.5 l are chosen for calculations shown below, with the understanding that the person is supine, and that "normal" volumes vary widely between individuals.

The **tidal volume** (V_T) is the volume of gas that passes in and out of the lungs with a single breath. As the volume of CO_2 excreted is smaller than the volume of O_2 taken up by the blood during normal metabolism (see Part 5-2, the respiratory quotient), the expired volume is therefore slightly smaller (4-5 ml) than the inspired. During quiet breathing at rest, a person of about 75 kg has a V_T of about 500 ml; during maximal depth of breathing (e.g. maximal strenuous exercise) the V_T constitutes the difference between the TLC and the Residual Volume (RV – see

below and fig. 4-6), i.e. 4-5 liters. More on tidal volumes in health and disease in Parts 4-3 and 4-4.

Tidal volumes and alveolar gas exchange.

When inhaling a normal V_T, only about 70% of the inspired gas volume reaches the alveolar gas space (fig. 4-8). At the start of each inspiration, the anatomical dead space is filled with the gas expired from the alveoli during the previous expiration. The first 150 ml of gas that enters the alveolar space during inspiration is therefore gas whose concentration of O_2 and CO_2 is close to that already within the alveolar space – a gas that has transferred part of its O_2 to the blood and contains excreted CO_2.

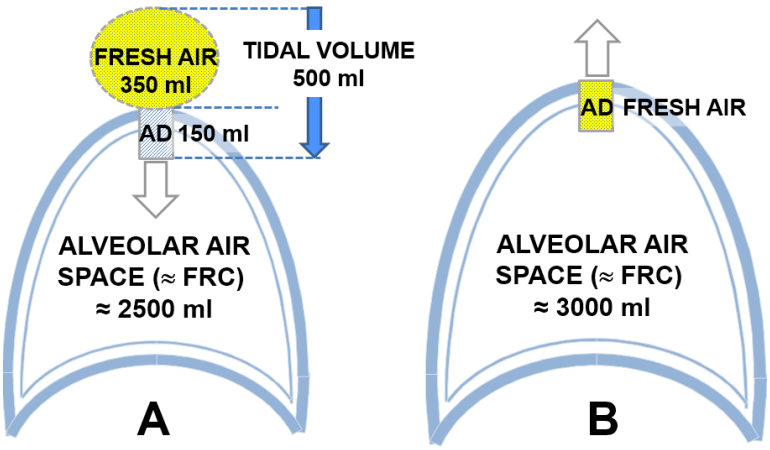

Figure 4-8. A. *During inspiration, a V_T of 500 ml consists of 350 ml of fresh air and 150 ml of the previously exhaled alveolar gas, filling the anatomical dead space* **(AD)**. **B.** *At end inspiration, the last 150 ml of inspired fresh air fills the AD, this gas is the first portion exhaled when expiration starts.*

The volume of *fresh gas* that mixes with the alveolar gas (i.e. with a volume approximately that of the measured FRC, see above) during a single inspiration of 500 ml air is then about 350 ml, which amounts to about 15-20% of a supine FRC (figs 4-5, 4-8). With a F_iO_2 of 0.209 (room air) and a V_T of 500 ml, this means a fresh supply of (350 ml x 0.209) = 73.2 ml O_2 with each breath; if the respiratory rate is 12/min, about 880 ml of fresh inspired O_2 enters the alveolar space each minute. As the resting $\dot{V}O_2$ is around 250 ml O_2/min, about 28% of the inspired O_2 is taken up by the blood during the resting state. If supplementary O_2 is added to the inspired gas (increased F_iO_2), smaller tidal volumes can maintain a normal alveolar PO_2. The excretion of CO_2, however, decreases when the TV decreases and the PCO_2 increases in proportion to the reduction in ventilation.

Effect of deep breathing on the alveolar gas. If the O_2 consumption increases, or if there is an uncompensated rise in the concentration of acids in arterial blood (see fig 4-9), the ventilation increases correspondingly. During breathing at maximal capacity, expiration continues until the residual volume is reached; almost all of the alveolar air is then replaced by fresh gas with every breath. The anatomical dead space stays the same; if the V_T is 4-5 liters, 96-97% of the inspired air reaches the alveolar space. The volume of fresh gas in each V_T then represents 350-400% of the residual volume, compared to about 15% of the FRC during quiet breathing - see gas volumes in fig. 4-6 above and the alveolar air equation below.

To keep the composition of the alveolar gas (and thus the blood gas levels) stable, fit adults may increase their minute ventilation during heavy exercise to about 90-110 L/min (35, 36); a minute ventilation of about 130 l/min may be maintained for a short period during heavy exercise (37).

The alveolar dead space.

The volume of gas ventilating alveolar areas that have *no perfusion* represents a*n alveolar dead space*, an increased alveolar dead space represents a corresponding reduction in the alveolar area available for gas exchange (Part 4-2). The ventilation of such areas is often called "wasted ventilation", as it contributes to neither oxygenation of the blood nor CO_2 excretion (38). In normal lungs, minimal- or no-perfusion conditions may exist in the upper part of the lung during quiet breathing in sitting or standing persons. Alveolar areas where such conditions exist have a variable size and may disappear completely when the pulmonary vascular pressures increases.

Physiological dead space. The anatomical and alveolar dead space in normal lungs is often lumped together as th*e physiological dead space* (39). As this gas volume consists of a constant (the anatomical dead space) and a variable (the alveolar dead space) compartment, the physiological dead space volume varies with perfusion (e.g. changes in C.O. and thus in the mean pulmonary artery pressure) and position changes.

Alveoli with reduced, or intermittent, perfusion may have a very high ratio between ventilation (V) and perfusion (Q). Even if some gas exchange takes place during part of the ventilation cycle, the changes are similar to those o*f pathological alveolar dead space* during the rest of the cycle. This latter type of alveolar hypoperfusion may increase during hypovolemia and ventilation with high airway pressures (see aslo Part 4-4).

Pathological alveolar dead space. In both acute and chronic lung diseases, the fraction of areas where the alveoli are ventilated, but only marginally (or not at all) perfused, is increased. As there is minuscule or no exchange of gas between the alveolar gas and the blood, the gas volumes ventilating such alveolar areas contribute little to the total pulmonary gas exchange.

Residual volume (**RV**). Even during *forced expiration,* it is impossible to empty the lungs of all air; the volume that remains at end of forced expiration (around 1.1 to 1.2 liters in normal lungs) represents the residual volume of the lungs.

The vital capacity (**VC**). The maximum gas volume that can be exchanged by the lungs (the maximum tidal volume) in one breath is the difference between the total lung volume at end inspiration and the RV. This volume is 3-5 liters in healthy persons (19, 40), it is considerably smaller in patients with emphysema (41) and may also be drastically reduced during severe asthma attacks (42).

Closing volume. The smallest airways have no structural support to keep them open when the volume of the lung decreases under expiration; when they close, the flow of air from alveolar areas distal to the occlusion ceases. During inspiration, they may not open immediately; the opening is delayed until the pulmonary gas volume reaches a critical level. The pulmonary gas volume where such airway closure occurs (the closing volume) becomes greater with age, and also increases as a result of pulmonary disease (43). When this happens, i.e. when the closing volume becomes larger than the FRC, the alveolar areas distal to such airways receive fresh gas, and expel alveolar gas, only during the part of the ventilation cycle when the small airway diameter is largest. This reduces the ventilation, leading to an increased number of alveoli with a low ventilation-perfusion ratio and reduced O_2 content (see Part 4-2).

THE PO_2 IN ALVEOLAR GAS: FROM AMBIENT AIR TO THE ALVEOLI

The composition of alveolar gas.

The PO_2 in the gas within the alveolar space differs from that in normal ambient air, as the latter is diluted by both water vapor and CO_2 after entering the airways. In addition, O_2 uptake*by* the blood and excretion of CO_2 *from* the blood changes the content of both gases in the alveolar gas space continuously. The alveolar ventilation volumes adjusts continuously to keep the alveolar concentration of both gases stable (see control of breathing below).

Exact measurements of gas composition within individual alveoli would be extremely difficult and would anyway not be representative of the whole lung, as there is considerable heterogeneity in alveolar ventilation between different areas also in healthy lungs (see below). The fraction of O_2 and CO_2 in gas samples from the last part of an expired tidal volume, th*e end-expiratory gas*, is considered representative of th*e mean* content of the gas in the various alveolar spaces in normal lungs. The pressures of O_2 and CO_2 in end expiratory gas from healthy lungs are considered to be close to, or equal with, their respective pressures in arterial blood. This doe*s not* hold true for patients with acute or chronic diseases of the lung (see Part 4-2).

The PO_2 of the alveolar gas (P_AO_2) is determined by the number of O_2 molecules per volume gas present in the alveolar airspace. In normal lungs, this number, and consequently also the P_AO_2 and P_aO_2, is modified by changes in

- **The composition of the inspired gas** (i.e. the fraction of O_2 in the gas), which may be the result of*either* addition of extra O_2 (increased F_iO_2)*or* displacement of O_2 in the inspired air by other gases (decreased F_iO_2).
- **The ambient barometric pressure, P_B**. With a normal fraction of O_2 in the inspired gas, the number of O_2 molecules and thus the PO_2 decreases at high altitudes and increases during diving below the surface of the sea.
- **The alveolar ventilation pattern,** i.e. the tidal volumes and respiratory rate, relative to the metabolic rate, determines the partial pressures of O_2 and CO_2 in the alveolar gas space.
- **The alveolar content of endogenous (or other) gases** that may displace part of the O_2 (CO_2, or a "second gas"). It is often associated with changes in **P_ACO_2** during hyper- or hypoventilation, as described by the alveolar gas equation (see below).

A *temporary* increase of gases released from the blood (e.g. nitrogen (**N_2**), when ascending after diving or during sudden decompression, *or* nitrous oxide (**N_2O**), when released from the blood after inhalation anesthesia with this gas, see second gas effect) may also displace parts of the O_2 in alveolar air, resulting in hypoxemia for a limited period.

The PO_2 in inspired air.

PO_2 in dry ambient air. The amount of O_2 in dry ambient air represents approximately 20.9%, or a fraction (**F_iO_2**) of 0.209, of the total volume of air. This fraction is independent of changes in the barometric pressure **(P_B)**; the oxygen pressure **(PO_2)** in **dry inspired air at sea level** (where the mean barometric pressure (P_B) is 101.3 kPa *or* 760 mmHg) is, therefore:

$PO_2 = P_B \times F_iO_2 =$ 101.3 kPa × 0.209 **= 21.2 kPa** *or* 760 mmHg x 0.209 = **159 mmHg**.

The total number of molecules in the air changes, however, with variations in barometric pressures, i.e. the number of O_2 molecules in ambient air changes in proportion to changes in the

barometric pressure. If the $\mathbf{P_B}$ *is reduced by 50%* (i.e. to 50.65 kPa, corresponding to an altitude of 5 500-6 000 meters (18 000-19 500 feet, see Table 4-1), the $\mathbf{PO_2}$ *in dry air* is

$\mathbf{PO_2 =}$ 50.65 kPa × 0.209 **= 10.6 kPa** *or* 380 mmHg x 0.209 = **79 mmHg**.

The effect of humidification on PO_2 in the inspired gas.

When the air is humidified, the water vapor pressure constitutes a part of the total gas pressure; the fraction of the gas volume occupied by water vapor is relative to the proportion between its gas pressure and the atmospheric pressure at the actual temperature.

If the *total gas pressure remains constant* , the water molecules displace part of the molecules of the other gases present, among them O_2. Regardless of the humidity of the inspired gas, the gas is moistened by the fluid layer on the surface of the airway mucous membranes and is 100% humidified when it becomes part of the alveolar gas (see above).

The water vapor pressure ($\mathbf{P_{H_2O}}$) at 37°C is about 6.3 kPa (47 mmHg); the **PO_2 in 100% humidified inspired air, $PO_{2\,hum}$,** at body temperature becomes:

$\mathbf{(P_B - P_{H_2O}) \times F_iO_2}$ = (101.3 – 6.3) kPa × 0.209 ≈ **19.9 kPa** *or* (760 – 47) mmHg x 0.209 ≈ **149 mmHg**.
As the $\mathbf{P_{H_2O}}$ is independent of ambient pressure, a P_B decrease to 50% will give

$\mathbf{PO_{2\,hum}}$ **=** (50.65 – 6.3) kPa × 0.209 ≈ **9.3 kPa** *or* **(**380 – 47) mmHg x 0.209 ≈ **70 mmHg**.

Utilizing the Alveolar Gas Equation to calculate PO_2 in the alveolar gas (P_AO_2).

When ventilation volumes decrease, fewer O_2 molecules enter the alveolar air space per minute. Without a corresponding reduction of the O_2 consumption, the P_AO_2, and thus also the P_aO_2, decreases. The efficiency of CO_2 excretion is simultaneously reduced; in normal lungs, the magnitude of the increase in P_ACO_2 correlates well with the reduction in P_AO_2. A normal tidal volume consists of about 70% fresh gas and 30% rebreathed alveolar gas (fig. 4-8), a change in the ratio between fresh and rebreathed gas also affects the mean P_AO_2.

An empirical equation for calculating the mean PO_2 in alveolar air, based on the effects of ambient pressure, F_iO_2, and P_ACO_2, was developed during the Second World War (44). The main goal of the scientists working on this project was to develop equations for estimating the effect of high altitudes on the O_2 content of alveolar gas, and thus on the P_aO_2, in aviators flying at high altitudes. The amount of supplementary O_2 necessary to ensure adequate arterial blood oxygenation could then be calculated.

The original, somewhat complicated equation has later been modified and simplified; the **commonly used version of the alveolar gas equation** today is

$$\mathbf{P_AO_2 = [(P_B - P_{H_2O}] \times F_iO_2 - P_aCO_2/RQ^*}$$

where the $\mathbf{P_aCO_2}$ is assumed to be close, or equal, to the $\mathbf{P_ACO_2}$.
***RQ** = The Respiratory Quotient, i.e. the ratio between CO_2 generation and O_2 consumption, which has a normal value of 0.8 in persons with a balanced western diet.

The **limitations** of such calculations must be recognized. The alveolar gas equation was developed and validated for persons with essentially healthy lungs, i.e. normal alveolar-capillary function during steady state conditions. In persons with pulmonary diseases and/or structural changes, *or* when other gases than normal concentrations of N_2 ("second" gas effect, see below)

are involved, the measured P_aO_2 may deviate substantially from the calculated P_AO_2. Under conditions where *extreme deviations* from normal values of F_iO_2, PCO_2 and P_B exists, the results may also be misleading.

To perform such calculations, it necessary to know the barometric pressure (usually assumed to be normal for most hospitals at sea level), the F_iO_2 (with reasonable accuracy, the flow of O_2 through open masks or catheters does usually *not* permit calculations of F_iO_2 in individual patients – see Part 4-4), and the PCO_2 in arterial blood. All parameters involved *and* the pulmonary gas exchange conditions must be in a steady state. The results may not be fully accurate but seldom deviate from the *measured* arterial PO_2 values by more than 1 kPa for normal lungs when the parameters involved in the calculation are within the physiological range.

In clinical medicine, the *importance of calculating the P_aO_2* is that a difference between this *calculated* value and the PO_2 *measured* in arterial blood indicates whether a reduced P_aO_2 is due to generalized hypoventilation with *increased PCO_2* (i.e. the function of the alveolar-capillary units are normal) or *dysfunction of pulmonary gas exchange* (i.e. dysfunctional alveolar-capillary units, Part 4-2). The normal difference varies, but is usually in the range of 0.5-1 kPa (4-7 mmHg)) (45) provided steady-state conditions exist. A (P_AO_2 - P_aO_2) difference smaller than 1-2 kPa (7.5-15 mmHg) is of little clinical significance. The *magnitude* of the alveolar-arterial difference (see below) is a measure of the *severity* of the gas exchange dysfunction; in severe pulmonary failure with a high F_iO_2, the difference may be more than 50 kPa (375 mmHg).

Calculation examples: P_AO_2 when breathing room air or 100% O_2.

Inserting normal values at sea level barometric pressure and **breathing room air**, the alveolar gas equation gives

P_AO_2 = $[(101.3 - 6.3) \times 0.209] - 5.3/0.8 \approx$ **13.23 kPa** *or* $[(760 - 47) \times 0.209] - 4\ 0/0.8 \approx$ **99 mmHg** if $P_aO_2 \approx P_AO_2$, corresponding to a S_aO_2 of ≈ 97.5%.

Hypoventilation reduces the P_AO_2 substantially, the level associated with a 100% increase in alveolar **PCO_2** to **10.6 kPa** becomes

P_AO_2 = $[(101.3 - 6.3) \times 0.209] - 10.6/0.8 \approx$ **6.6 kPa** *or* $[(760 - 47) \times 0.209] - 80/0.8 \approx$ **50 mmHg** if $P_aO_2 \approx P_AO_2$, corresponding to a S_aO_2 of ≈ 85%.

When **breathing 100% O_2 (F_iO_2=1.0)** instead of room air for a period long enough to eliminate virtually all N_2 from the alveolar air, the calculation of P_AO_2 *with normal ventilation volumes* and P_aCO_2 would result in

P_AO_2 = $[(101.3 - 6.3) \times 1.0] - 5.3/0.8 \approx$ **88 .4 kPa** *or* $[(760 - 47) \times 1.0] - 40/0.8 \approx$ **663 mmHg** if $P_aO_2 \approx P_AO_2$, corresponding to a S_aO_2 of ≈ 100%.

The reduction in *P_AO_2 during hypoventilation* with a 100% increase of arterial and alveolar PCO_2 when breathing pure O_2 would be without clinical importance:

P_AO_2 = $[(101.3 - 6.3) \times 1.0] - 10.6/0.8 \approx$ **81. 8 kPa** *or* $[(760 - 47) \times 1.0] - 80/0.8 \approx$ **613 mmHg**. If $P_aO_2 \approx P_AO_2$, i.e. there is *no clinical effect* of such a PCO_2 increase on the S_aO_2.

After calculation of the P_AO_2, the difference between calculated P_AO_2 and measured P_aO_2 provides an objective foundation for the estimation of changes in the capacity of the alveolar-capillary units of the lungs to transfer O_2 from gas to the blood (see Shunt and V/Q disturbances, Part 4-2).

Simplified calculation of alveolar PO_2.

A simplified **"quick and dirty" bedside calculation of the P_AO_2** without technical aids may be done for patients at sea level if the P_aCO_2 does not deviate more than 1-2 kPa from the normal value. The method below is intended for rough bedside estimation, and should not be used as a scientific tool.

When gas pressures are expressed in kPa, and the F_iO_2 is known, an approximate P_AO_2 can be calculated as

P_AO_2 (expressed in **kPa**) ≈ [**O_2 in the inspired gas,** expressed in **%**] **– 10**

The rationale for such calculations is that

- As the normal atmospheric pressure at sea level is 101.3, the PO_2 in the inspired gas will be *almost the same* as the O_2 percentage.
- The sum of the *water vapor* and the *CO_2 pressure,* corrected for the fact that the former is deducted from the atmospheric pressure before multiplication with the O_2 fraction in the alveolar gas equation, is close to 10 kPa. If the CO_2 pressure is substantially increased, reasonable accuracy can be maintained by deducting also the excess P_aCO_2 (the increase above normal value) in kPa.

With corrections as above, the error caused by using the "quick and dirty" method will, in general, be within 2% of the value calculated by the alveolar air equation. Calculation examples (values calculated using the "classical" alveolar gas equation are shown in parenthesis):

With a **F_iO_2 of 0.4** and **normal P_aCO_2:** $P_AO_2 \approx 40 - 10 = 30$ kPa (31.3 kPa).
With a **F_iO_2 of 0.7** and **normal P_aCO_2:** $P_AO_2 \approx 70 - 10 = 60$ kPa (59.9 kPa).

With a P_aCO_2 **increase to ≈ 10 kPa,** the calculation becomes:

With a **F_iO_2 of 0.4:** $P_AO_2 \approx 40 - 15 = 25$ kPa (25.5 kPa).
With a **F_iO_2 of 0.7:** $P_AO_2 \approx 70 - 15 = 55$ kPa (54.0 kPa).

The mechanisms determining the alveolar PCO_2.

The CO_2 molecules generated by the aerobic metabolism in the tissue cells diffuse through the interstitium into the microcirculatory blood as dissolved gas; after entering the erythrocytes, they are subsequently transported to the lungs either as *dissolved gas* (measured as PCO_2), as *bicarbonate ions*, or as CO_2 *chemically bound to the Hb* molecule (carbamino compounds, not routinely measured), see Part 2-3 for details. As long as new CO_2 is generated in the tissues, the pressure of CO_2 in mixed venous blood is always higher than that in alveoli and the CO_2 diffuses freely from the blood into the alveoli along a gas concentration gradient. The amount of CO_2 exhaled per minute under resting conditions represents about 8% of the total CO_2 content of the blood. This functions as a buffer against rapid changes in blood P_aCO_2.

When the venous blood reaches ventilated alveoli, the PCO_2 in the venous blood is slightly higher than that in the alveolar gas (i.e. ≈ 6 kPa (*45 mmHg*) vs ≈ 5.3 kPa (*40 mmHg*)). The CO_2 diffuses into the alveoli along this gradient, the CO_2 concentration in plasma and within erythrocytes fall; the intra-erythrocyte reaction occurring in the tissues is reversed (*dehydration* of H_2CO_3) and runs to the left (see also Part 5-2):

Most of the H^+ ions involved in this reaction are released from their binding sites on the Hb molecules, which then increase their affinity for O_2 (see Part 2-3).

The PCO_2 in the alveolar gas (**P_ACO_2**) is determined by

- The **volume of CO_2 generated in the tissues,** which, under normal circumstances, is a function of the aerobic metabolic rate.
- The **volume of CO_2 delivered to the lungs by the venous blood** per unit of time; which is a function of *both* the rate of *CO_2 generation* and the *blood flow.*
- The **efficiency of the CO_2 excretion**, i.e. *i)* the capillary-alveolar gas exchange *gradient* , *ii)* the total *alveolar ventilation*, *and iii*) the total *surface of alveolar-capillary units* and their ventilation-perfusion conditions.

In persons with normal respiratory function, tidal volumes and respiratory frequency adapt to a wide variety of metabolic- and blood flow rates; this regulation is so effective that alveolar CO_2 pressure (P_ACO_2) (as deducted from arterial and end-tidal PCO_2) remains relatively constant regardless of CO_2 production rates and venous PCO_2.

The "second gas" effect on P_AO_2.

A special type of oxygenation problem may arise when gases like nitrogen (liberated from blood and tissues during ascent after diving) and nitrous oxide (given as part of the inspired gas during anesthesia) diffuse rapidly into the alveoli from the blood and displace part of the O_2 (called "diffusion hypoxemia" or "second gas effect", see below). These situations represent an unstable condition with rapid changes in the concentration of the second gas; as the alveolar gas equation does not include the effect of such gases, the difference between the P_AO_2 as calculated from the alveolar air equation, and the measured P_aO_2, may be substantial even when the lung function *per se* is normal.

In persons able to increase their depth of ventilation in response to hypoxemia, and thus the rate of elimination of the second gas, such problems are self-limiting and seldom cause serious oxygenation problems (46, 47, 48). Hypoventilation during such conditions may, however, accentuate the problem and may lead to severe hypoxemia (49) if the F_iO_2 is not increased.

Pulmonary reserves of O_2 during apnea and respiratory arrest.

Apnea may be voluntary (breath-holding, see below), involuntary (e.g. respiratory arrest due to cerebral anoxia, damage to the upper cervical medulla spinalis, intoxications, muscle relaxants, etc.), *or* be due to upper airway occlusion (e.g. strangulation, see Part 4-3).

Reserves of alveolar O_2 during voluntary breath-holding. At the start of such maneuvers, the subjects usually draw a deep breath and fill their lungs to vital capacity. The large tidal volume increases the amount of O_2 added to the alveolar air, increasing the P_AO_2 to levels *above* normal for a limited period. If we *conservatively* assume an *at least* normal P_AO_2 of 13.3 kPa (100 mmHg), the **fraction of O_2 in this alveolar gas is P_AO_2/P_B** (13.3 kPa/101.3 kPa) ≈ **0.13**. In a person breathing room air at sea level, with a VC of around 5.0 liters, the **reservoir of O_2** available for gas exchange with the blood (i.e. the alveolar gas volume) is then

5 l (volume of alveolar gas at VC) **x 0.13** (liter of O_2/l alveolar gas) ≈ **0.65 liters of O_2.**

corresponding to around 2.5 minutes of resting O_2 consumption. At the start of apnea, this reserve comes in *addition to the O_2 in the blood*, of which 20-25% of the blood volume (around 1 liter) may be assumed to contain blood with an O_2 content similar to the arterial blood, i.e. 0.2 liter O_2. The remaining blood volume has a mean O_2 content similar to that in mixed venous

blood (around 150 ml O_2/l, i.e. 0.6 liter O_2). The increase in PCO_2 during this period would be around 2 kPa (15 mmHg).

Reserves of alveolar O_2 during respiratory arrest. At the start of apnea following sudden cessation of ventilation, the gas volume within the lungs rapidly approaches a volume equal to the FRC. If the person had been breathing room air until the respiratory arrest occurred, and the supine alveolar gas volume of the person is approximately 2 liters, the reservoir of O_2 available for gas exchange by the blood is

2 l (volume of alveolar gas) **x 0.13** (liter O_2/l liter alveolar gas) ≈ **0.26 liters of O_2,**

which corresponds to about 1 minute of baseline O_2 consumption.

After the onset of respiratory arrest, the P_aO_2 will decrease continuously and reach levels of severe hypoxemia before a minute has passed; recordings during sleep apnea show that the S_aO_2 decreases by approximately 24% after 42 sec. of apnea (50). It must be emphasized that the above calculation examples are valid for sleep or resting conditions only; stress and muscular contractions ("fighting for breath") during airway occlusion in awake persons increase the $\dot{V}O_2$ substantially and decrease the apnea time before start of tissue hypoxia dramatically.

On the other hand, trained divers may be able to hold their breath for several minutes while free-diving or during static apnea; the present world record for static apnea (i.e. breath-holding with no use of limb musculature) is about 9 minutes for women and 11 minutes for men (51). The total lung capacity of individuals that compete successfully in breath-holding contests is 8-10 liters (see above), which may be augmented further when a "buccal pumping" maneuver (52) is employed. Such persons may have a reservoir of 1.3 to 1.5 liters of O_2 in the lungs at the start of apnea after breathing room air; they can also suppress the involuntary contractions of the diaphragm as CO_2 increases. The breaking point for terminating apnea in such persons occurs when the S_aO_2 gets close to 50% (52), which occurs after 10-12 min in highly trained apneists. If trained apneists breathe 100% O_2 before the start of the apnea, an apnea time of more than 24 minutes has been recorded (53).

Much is known about the physiological adaptions that make dives of long duration possible in animals (54), some of the adaptions of trained humans to cold-water immersion and breath-holding are similar (e.g. bradycardia, diversion of blood flow to favor the most O_2-sensitive organs, spleen contraction). Genetic adaptions of metabolic processes during diving in special populations may exist (55), but have not been fully elucidated.

In a person *breathing 100% O_2 for some minutes before breath-holding* at vital capacity, but keeping the ventilation volumes and thus the P_ACO_2 normal, the P_AO_2 as calculated by the alveolar air equation is 88.4 kPa (663 mmHg). The **fraction of O_2 in this gas is P_AO_2/P_B** (88.4 kPa/101.3 kPa) ≈ **0.87**, calculations corresponding to those above will return an available volume of O_2 equal to **5 l** (volume of alveolar gas) **x 0.87** (liter O_2/l liter gas) ≈ **4.36 liters of O_2** at body temperature before the start of breath-holding at maximal lung capacity. At the start of involuntary apnea with the alveolar gas volume close to an FRC of **2 l**, the calculation becomes **2 x 0.87** (liter O_2/l liter gas) ≈ **1.75 liters of O_2.**

In patients with acute, severe lung disease, the FRC may be reduced by more than 50% of normal values (56); the O_2 reserves in alveolar gas during apnea, and thus the apnea time before grave hypoxemia, are reduced correspondingly.

CONTROL OF SPONTANEOUS BREATHING

Automated control of breathing takes place primarily in the brain stem (*medulla oblongata*). Other parts of the brain also play a part in the control of breathing, but the center in the brain stem is the most important one. The cerebrum can, to some extent, override the automatic ventilation pattern from the brain stem. The respiratory center receives signals from various central and peripheral *sensors* (including chemoreceptors, see below), which report back on the state of the lung tissue itself, the pH of the arterial blood, and its O_2 and CO_2 content. For more details on the neurogenic control of breathing, see refs 57, 58, 59.

Peripheral chemoreceptors

are located in the aortic arch and the carotid artery. The latter, the **carotid bodies**, are probably the most important in humans. They have a very high perfusion flow, and **monitor changes in pH, PCO_2, and PO_2 in arterial blood**; an *increase in $PaCO_2$*, and/or a *decrease in pH* or *PaO_2* leads to increased ventilation. Hypoxia is a powerful stimulus for the peripheral chemoreceptors but has a depressant effect on the central respiratory centers (see below). Especially in *premature babies*, a *paradoxical response to hypoxia* may be seen, with respiratory *depression* instead of respiratory *stimulation* (60).

Central chemoreceptors

consist of cell clusters located in the brain stem, immediately beneath the brain stem surface, and in close contact with the cerebrospinal fluid (**CSF**). The CSF is separated from the blood by the so-called *blood-brain barrier* (the barrier function is due to the low permeability of brain capillaries to most molecules other than nutrients, water, and gases). The main stimulus for this center is **the pH of the CSF.** Acute pH changes in the blood have little impact on the central chemoreceptors, as both H^+ and HCO_3^- ions pass the blood-brain barrier very slowly. However, CO_2 diffuses rapidly from blood to CSF without hindrance; an increase of CO_2 in the blood will result in a similar increase of CO_2 in the CSF. A small part of the increased CO_2 is converted to H^+ and HCO_3^- ions (although at a much slower rate than in blood, as the CSF contains no carbonic acid anhydrase – see Part 5-2), and thus produces a secondary increase of H^+ and a falling pH in the CSF. An increase of CO_2 in the blood will therefore stimulate the respiratory center to increase ventilation also through its action

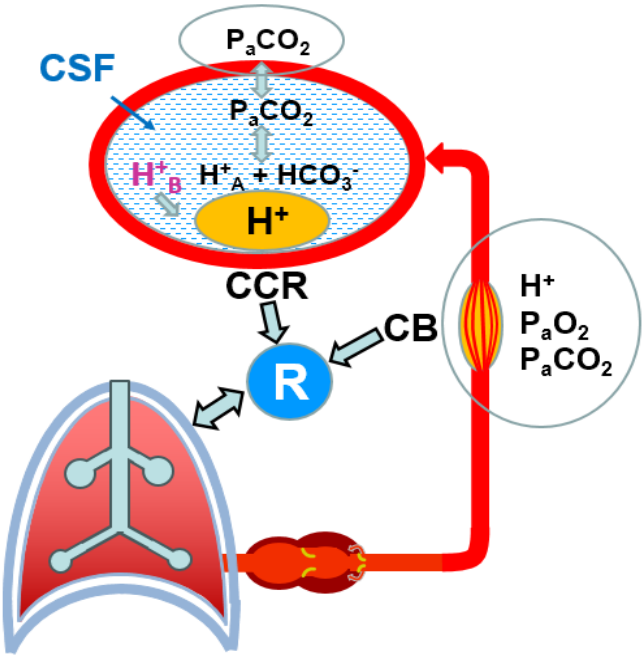

Figure 4-9. *The respiratory control centre* **(R)** *integrates signals from the chemoreceptors in the well-perfused carotid bodies* **(CB),** *the central chemoreceptors* **(CCR-**yellow**)** *and the lung tissue. The carotid bodies monitors pH, PO_2 and PCO_2 in the arterial blood, while the central chemoreceptors monitor the pH in the cerebrospinal fluid* **(CSF)**. *The latter is determined by the level of PCO_2 in arterial blood* **(H^+);** *injury to brain tissue may also release acid metabolites* **(H^+_B)**.

on the central chemoreceptors. Local, metabolic changes in the brain that result in a pH decrease in the CSF (as in brain tissue damage, hemorrhage, etc.) can also stimulate ventilation through their action on the central chemoreceptors. In such conditions, a seemingly unexplained respiratory alkalosis (see Part 5-3) in the arterial blood may be found.

Opposite effects on peripheral and central chemoreceptors in metabolic acidosis.

An increase in P_aCO_2 stimulates both peripheral and central chemoreceptors, leading to increased ventilation. However, metabolic acid-base changes may produce an opposite effect on the two types of receptors. The initial acute increase of arterial H^+ ions is detected by the carotid body receptors, which send signals to increase ventilation. When the PCO_2 of the blood falls, PCO_2 in the CSF also decreases, which reduces the H^+ ion concentration (*rise in pH*, *CSF alkalosis*) around the central chemoreceptors. This local CSF alkalosis sends inhibitory signals to the respiratory center and prevents complete respiratory correction of metabolic acidosis (see also Part 5-2).

Receptors in the lung tissue.

The lung tissue also contains receptors that give off signals to the respiratory center. *Stretch receptors* (slowly- and rapidly adapting) are found among smooth respiratory tract musculature, while *irritant receptors* are located between the epithelial cells in the airways and react to irritant gases, dust and cold (61, 62). *J receptors* are found in the alveolar walls and may be activated by pulmonary congestion and the formation of edema in the lungs

THE PULMONARY CIRCULATION

Blood vessels of the lungs

The pulmonary circulation is a valveless, low-pressure system where also the arteries have thin walls and high compliance; normal pulmonary vessels are highly distensible and are readily dilated by increased pressure. The **pulmonary arteries** carry the mixed venous blood to the alveolar compartments, while the **pulmonary veins** collect the oxygenated blood. A few percent of the circulating blood passes directly from the right to the left side of the heart (mostly through bronchial vessels) without being exposed to alveolar air (63); under normal conditions, the magnitude of such flow is about 2% of the total and has only a minimal (approximately 0.5%) impact on the arterial O_2 content.

Normal pressures in the lung vessels.

Normal pressure in the pulmonary artery (**PAP** = Pulmonary Artery Pressure) is about **25/10 mmHg**, with an average pressure (mean pressure, **MPAP**) of about **15 mmHg**. The PAP represents the resistance against ejection for the right ventricle; at the bedside, it may be measured with the aid of a *pulmonary artery catheter* (PAC, Swan-Ganz catheter) or calculated from measurements obtained by *echo-doppler cardiography* (ECHO) (see also Part 3-4).

Pulmonary vascular resistance.

The total venous return (equal to the C.O. in the absence of anatomical aberrations) passes through the lungs. The perfusion pressure in the pulmonary vascular bed is the mean pulmonary arterial pressure (MPAP) minus the mean pulmonary venous pressure (MPVP) or PCWP, which is close to the mean left atrial pressure. Analogous to the systemic circulation (see also Part 3-1),

the pulmonary vascular bed resistance (**PVR**) is calculated by dividing the perfusion pressure by cardiac output (C.O.), or

PVR = (MPAP — PCWP)/C.O. (see Apx for units).

The *indexed* resistance is calculated by dividing by the CI instead of C.O. Due to the normally low pressures in the pulmonary circuit, the PCWP in healthy persons is about 40-50% of the MPAP, and cannot, as in the systemic circulation, be excluded from the equation for bedside simplification purposes.

The **PVR** in normal lungs has been found to be distributed as about 46% in arteries and arterioles, 34% in the capillaries, and 20% in the veins (64). As normal pulmonary vessels are easily distensible, a substantial increase in C.O. results in only a modest increase in MPAP. When the C.O. increases, the calculated PVR of normal lungs is therefore reduced. A "normal" PVR in the face of increased C.O. signals a decrease in the total distensibility or compliance of the pulmonary vasculature.

Hypoxic pulmonary vasoconstriction – HPV.

Alveolar hypoxia is a powerful stimulus to contraction of the precapillary arteries at the acini level. This mechanism reroutes blood flow to acini with better ventilated alveoli, which improves the gas exchange. At high altitudes, breathing gas with a reduced O_2 content may cause a generalized contraction of such vessels and increase the total pulmonary vascular resistance (65). As in the systemic circulation, *sympathetic nerve stimulation* and selective *stimulation of* α_1 *receptors* cause vasoconstriction in experimental animal models (66, 67) and human vessels *in vitro* (68). Various vasoconstricting agents may, however, have different effects on pulmonary and peripheral vessels (68).

The O_2 and CO_2 in mixed venous blood in the pulmonary artery represent an average value of the content in venous blood from all organs. Analysis of such blood provides information about the O_2 and CO_2 balance of the body *as a whole* but provides no information about the balance *within* individual organs.

The pulmonary microcirculation.

This part of the pulmonary circulation may be divided into *pre-alveolar, alveolar,* and *post-alveolar* vessels; animal investigations (cats) have shown that each precapillary vessel supplies blood to approximately 25 alveoli, while the postcapillary vessels drain blood from about 18 alveoli (69). The pulmonary capillaries, in which the blood comes into close contact with the gases in the alveoli, are a network of small, extremely thin-walled, and inter-communicating vessels (see also fig. 4-1 above). The network does not consist of separate vessels; the capillaries communicate with each other at many points during the passage of the blood past the alveolar gas. The blood flowing through a capillary may pass through 5-7 alveoli before exiting the areas of gas exchange; the mean period of contact between each erythrocyte and the alveolar gas is around 0.8 seconds (70). The blood flow through the alveoli has been compared to a film or sheet of blood flowing through the alveolar walls and septa (71).

The blood is conducted to, and drained from, the alveolar areas by the *extra-alveolar vessels*; which pass through connective tissue sheaths, through which minor lymphatic vessels and small airways also pass (fig. 4-1). Most, if not all, of the fluid seepage due to hydrostatic forces from the pulmonary microcirculation occurs from these vessels. If the seepage is greater than the

capacity for drainage of lung lymph, interstitial pulmonary edema arises; such edema may compress the small airways passing through these structures and cause hypoventilation of the alveolar areas supplied by these airways. If the pressures of this edema fluid within the interstitial space increase further, the fluid spills over into the alveolar space, and frank alveolar edema may develop.

Distribution of the blood flow within the lungs

Due to the lack of valves, the distribution of blood is, to a large extent, determined by the gravitational force, the hydrostatic pressure is influenced by the position of the vessel relative to the level of the heart. Above heart level, the pressure distending the vessels decrease with increased elevation; and *vice versa* for vessels below heart level. As tubes with a large diameter accommodate a higher flow than those with a smaller, a larger percentage of the total blood flow passing through the lungs perfuse the vessels situated lowest relative to the heart. Those differences in perfusion are most important in the upright position; the differences relative to the heart are smaller when in the supine or prone position.

The hydrostatic pressure in the vessels of a given part of the lungs depends on three factors:

- **The pulmonary arterial pressure,** which is determined by ***i)*** cardiac output, ***ii)*** blood viscosity, and ***iii)*** total elastance/resistance of the pulmonary vascular bed.
- **The left atrial pressure**, which is controlled by ***i)*** pulmonary blood flow, ***ii)*** left ventricular compliance and contractility, and ***iii)*** mitral valve function.
- **The elevation of the vessels relative to the heart;** this is altered when the position of the body (upright, supine, or prone) changes.

In addition, local differences in vascular dimensions and variations in the state of contraction (or in the degree of obstruction or occlusion) of vessels may affect the distribution of pulmonary blood flow (see below).

During spontaneous ventilation, the gas pressure in the alveoli oscillates around 0 cmH_2O, while the hydrostatic pressure in the uppermost pulmonary vessels may become slightly negative. During expiration, the gas pressure in the alveoli surrounding the pulmonary capillary network may therefore become higher than the capillary hydrostatic pressure in these areas and compress the capillaries. When this happens, the blood flow in the microcirculation may slow or stop during part of the ventilation cycle, creating an *intermittent alveolar dead space*. Increased flow (i.e. increased C.O.) augments the intravascular pressures and ensure perfusion also of the uppermost part of the lungs. These areas represent a perfusion reserve, to be recruited and thus increase the area of alveolar gas exchange when the PAP and/or the PVP increases (72).

In conditions in which the pulmonary vessels become more rigid (as in primary pulmonary hypertension, COPD, or ARDS, see Part 4-3), or when the number of functioning vessels in the microcirculation has been drastically reduced (e.g. in emphysema, pulmonary embolism, resection of lung tissue), increased cardiac output will produce significantly greater pressure in the pulmonary vessels. High pulmonary vascular pressures, regardless of etiology, result in increased afterload for the right ventricle. If permanent, they lead to RV hypertrophy and may, in the worst case, induce right ventricular failure. Very high pressures in the vessels remaining open during massive pulmonary embolization may also cause edema formation in the lung tissue that is *still perfused* while other areas remain under- or non-perfused.

The three zones of perfusion - West's model.

Based on experimental measurements, the physiologist West and co-workers (73, 74) proposed a division of the pulmonary circulation of an upright person into three zones:

Zone 1 (the upper zone), in which the pressure in the pulmonary vessels is so low that the gas pressure in the alveoli during expiration is higher than the pressure in the microcirculation on both the arterial and the venous side ($\mathbf{P_A > P_a > P_v}$). In a sitting or standing person, this zone may include a substantial area in the upper part of the lung. In the supine position, the gravitational differences in vascular pressures are less pronounced and this zone may become small or non-existent.

Zone 2 (the middle zone), in which the pulmonary vascular pressure on the arterial side is higher than the airway pressure in the alveoli, which in turn is higher than the pressure in the microcirculation on the venous side ($\mathbf{P_a > P_A > P_v}$). This creates a "waterfall effect", where the magnitude of the P_V has no impact on the perfusion.

Zone 3 (the most dependent zone), in which the pressure in the microcirculation on both the arterial and the venous side is higher than the airways pressure in the alveoli ($\mathbf{P_a > P_v > P_A}$).

Some experimental data suggests that there may be a **zone 4** at the very bottom of the lung (75), in which the circulation again become reduced because the weight of the lung tissue above increases the tissue pressure, which again compresses the vessels.

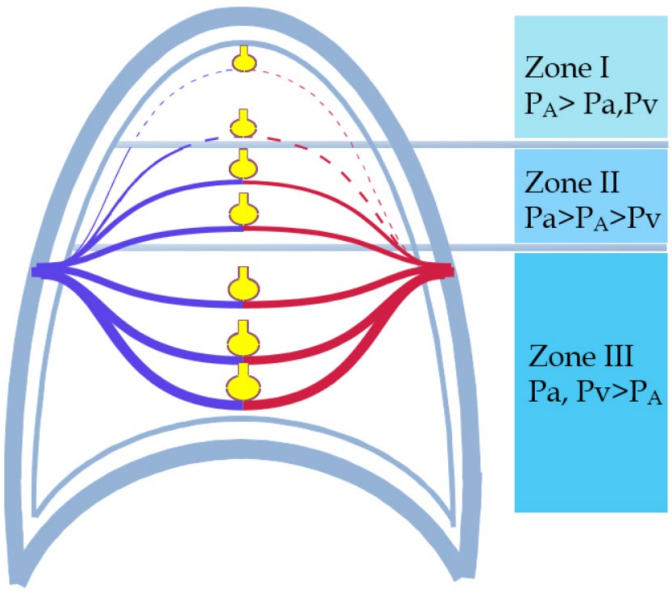

Figure 4-10. *The three zones of pulmonary perfusion conditions, according to West (see text).*

There is also experimental evidence to suggest that other factors in addition to gravity regulate the distribution of the blood in the lungs. While important in the upright position, gravity has a much smaller impact in the supine or prone position. The properties and geometry of the pulmonary vessels in different parts of the lung vary, and there are also differences in perfusion within the same horizontal plane of the lungs. The average perfusion is perhaps increased in the dorsal part compared to the ventral part of the lung; also, the distribution of flow varies with lung volume (i.e. the state of inflation) (76, 77). The main features of West's model probably hold true but may represent a somewhat simplified picture of a more complicated reality.

Fluid balance in the lungs

As in systemic capillary beds, there is a continuous seepage of fluid from the blood (see Part 2-2). The maximal transport capacity of the lung lymphatic system, extrapolated from animal experiments, is somewhere between 5 and 10 times the net quantity of fluid that normally is filtered

out of the pulmonary microcirculation (78, 79, 80). If the volume of the filtered fluid exceeds this transport capacity, **interstitial edema** develops; as the interstitial pressure increases, small airways located within these spaces are compressed, increasing the airway resistance and resulting in wheezing respiration ("cardiac asthma"), which may progress to **alveolar edema** (see Part 4-3).

THE ALVEOLAR VENTILATION-PERFUSION (V/Q) RATIO IN NORMAL LUNGS

The optimal condition for pulmonary gas exchange, taking both the O_2 supply *to*, and CO_2 excretion *from* the blood into consideration, probably occurs when the ratio between inspiratory gas flow (V) to the alveoli and their capillary perfusion flow (Q) is close to 1:1, i.e. the mean V/Q ratio is close to 1. At sea level, this ratio will ensure a P_aO_2 that gives a close to optimal O_2 saturation of the Hb molecules at rest.

A V/Q ratio of 1 is, however, mostly representative of the middle part of the lungs. In healthy lungs, the V/Q ratio is *higher in the apical part* of the lungs and *lower in the most dependent part*; ranging from approximately 3.0 to 0.8, respectively (81). The upper value is expected to result in an alveolar PO_2 of approximately 17.3 kPa (130 mmHg), the lower of approximately

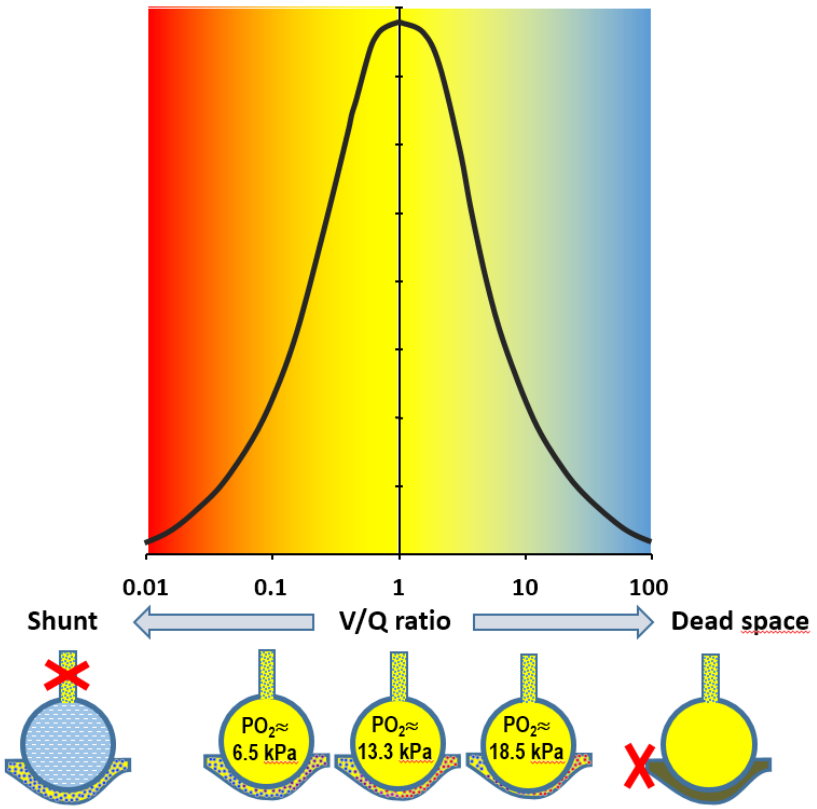

Figure 4-11. *Schematic plot of the heterogeneous distribution of alveolar areas with various V/Q ratios in healthy lungs. Gas exchange in areas with ratios below 0.01 behave as shunts, while those with ratios above 100 behave as alveolar dead space (see text). Alveolar PO_2 levels, calculated according to ref (83) for alveoli with V/Q ratios of 0.1, 1, and 10, are shown. See Part 4-2 for definitions of shunt and dead space. In pulmonary disease, the position, as well as the shape, of the V/Q distribution curve changes.*

12.4 kPa (93 mmHg) (82, 83). As the difference in SO_2 in the blood corresponding to those PO_2 values is less than 2%, the consequences of such differences for the O_2 content of the arterial blood are minuscule (see Part 2-3). The V/Q distribution is heterogeneous also within the same gravitational plane, with most (>95%) of the areas having a V/Q ratio between 0.3 and 2.1 (84). The calculated alveolar PO_2 with a V/Q ratio of 0.3 is around 9 kPa (67 mmHg), corresponding to SO_2 in the blood of around 93%. The arterial PO_2 represents the weighted mean of all pulmonary veins from various alveolar areas exiting the lungs. Thus, in terms of the O_2 content of the perfusing capillary blood, the difference between V/Q ratios of 0.3 and 3.0 has a substantial impact on local alveolar PO_2 but has only modest consequences for the O_2 content of the arterial blood (see fig 4-11 for the normal lung V/Q distribution).

When alveolar ventilation becomes *much* larger than the perfusion, the P_AO_2, and thus the PO_2 in the perfusing capillaries, also increase. When the alveolar V/Q ratio approaches 10, the O_2 concentration, and thus the PO_2 in the alveolar air, becomes close to that in the inspired air (i.e. 19.9 kPa or 149 mmHg, see calculations above). The contribution of such hypoperfused alveoli with a high P_AO_2 to the total O_2 content of the pulmonary blood flow is, however, very small, and such alveoli excrete almost no CO_2. During extreme muscular exertion, the capacity for increasing alveolar ventilation exceeds the capacity for increasing the cardiac output (see Part 3-1, Reserve capacity of the normal heart), and the mean V/Q ratio increases.

Other types of change in the mean V/Q ratio, especially those involving increasing heterogeneity of this ratio between alveolar areas, lead to increasing disturbances in the gas exchange. Such changes may have consequences for the O_2 and CO_2 content of the blood in disease. As a rule of thumb, an increase in alveolar regions with *low alveolar V/Q ratios* results in *hypoxemia,* while an increase in regions with *high V/Q ratios are associated with less efficient CO_2 excretion and hypercarbia* unless the total ventilation increases. A leftward shift in the curve in fig. 4-11 reduces the P_aO_2, a rightward shift increases the P_aCO_2.

Blood that flows through alveolar areas that cannot add any O_2 to the venous blood (e.g. fluid-filled alveoli, atelectasis, occluded airways) represents a **shunt flow** (V/Q=0). The blood perfusing such areas exits from the alveolar areas with the same PO_2/SO_2 and PCO_2 as that in mixed venous blood. Ventilated, but not perfused, alveolar areas represent an **alveolar dead space** (V/Q=∞), there is no gas exchange between alveolar gas and blood. See Part 4-2 for details, mechanisms and consequences in disease.

4-2. HYPOXEMIA, HYPERCARBIA, AND ALVEOLAR VENTILATION IN NORMAL AND DYSFUNCTIONAL LUNGS

Hypoxemia signifies a condition where the P_aO_2, *or* the SO_2, is significantly lower than normal. Arterial PO_2 decreases when increased shares of the mixed venous blood becomes only *partly* oxygenated after passing through lung regions where the alveolar-capillary units may be normal, but the alveolar gas has a subnormal PO_2. Common causes of reduced P_AO_2 are ***i)*** hypoventilation, which is also accompanied by increased P_ACO_2, ***ii)*** a reduced amount of O_2 in the inspired gas (see below). An even greater P_aO_2 decrease occurs when increased parts of the mixed venous blood perfuse lung regions where the alveoli have very low V/Q ratios, where the alveolar PO_2 is equal to the venous (i.e. alveoli situated distal to an airway occlusion), or contains no gas (e.g. fluid-filled or collapsed alveoli). Blood that perfuse the two latter type of regions leave the area with a PO_2 *equal to* that of mixed venous blood. Right-to-left shunts in the central circulation or the heart may cause severe hypoxemia even with normal lung function (see below and Part 3-3).

There is no international consensus about how to define hypoxemia (85); various investigators and guidelines define the term in different ways (86, 87). Commonly used definitions of hypoxemia are a $\mathbf{P_aO_2 \leq 8\ kPa}$ (60 mmHg) (88, 89) *or* a $\mathbf{S_aO_2}$ or $\mathbf{S_pO_2 < 90\%}$ (90), **severe hypoxemia** is often defined as $\mathbf{S_pO_2}$ or $\mathbf{S_aO_2 < 85\%}$ (91, 92). Hypoxemia when breathing normal air (i.e. $F_iO_2 = 0.209$) at sea level is a sign of ventilatory or gas exchange dysfunction if circulatory left-to-right shunts (see below) can be excluded (see below). It also occurs in persons with normal lungs if the mass of O_2 molecules in the inspired gas is reduced by low ambient pressures, or if an increased concentration of other gases in the alveolar air dilutes the O_2 (see Part 4-1, alveolar gas).

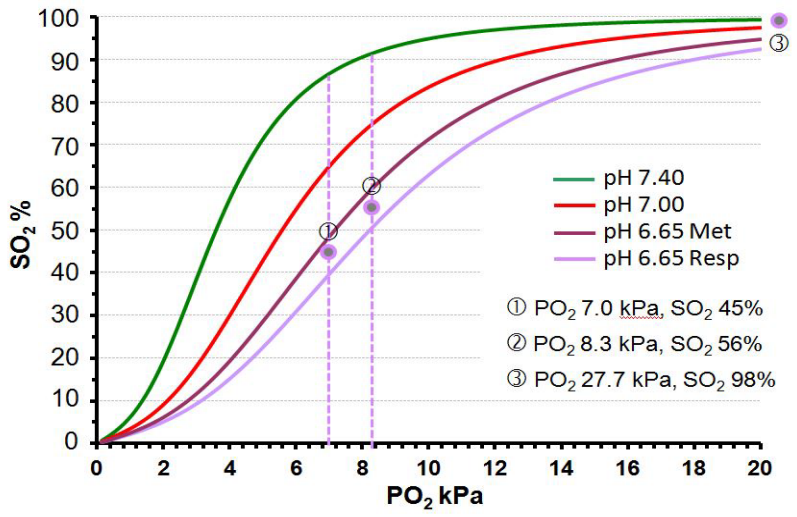

Figure 4-12 *Importance of discriminating between P_aO_2 and S_aO_2 when defining hypoxemia, and of establishing a high PO_2 in hyper-acute emergencies. Data from a patient with life-threatening bronchospasm and a combined respiratory and metabolic acidosis with an initial pH of 6.65 illustrate the point. The calculated HbO_2 dissociation curve for this pH when caused by metabolic (Met) and respiratory (Resp) acdosis are shown. HbO_2 curves for pH of 7.40 and 7.00 are shown for comparison. Circles indicate the results of the actual PO_2 and SO_2 values in arterial blood in three ABG samples taken sequentially during the first 15 minutes after admittance, ① and ② with O_2 on face mask, ③ after intubation and with 100% O_2.*

Hypoxemia must not be confused with the term *hypoxia*. In *hypoxemia*, the reduced O_2 content of the arterial blood may still be sufficient to sustain normal aerobic metabolism. Even severe hypoxemia may be compatible with adequate tissue oxygenation as long as the Hb is normal or elevated, and an adequate increase in C.O. can be mounted. In *hypoxia*, the O_2 supply to the tissues is *too low* to sustain aerobic conditions, regardless of etiology.

Consequences of hypoxemia for tissue oxygenation.

With a standard HbO_2 dissociation curve, a PO_2 of 8 kPa corresponds to an SO_2 of 91%, such mild hypoxemia in a person with a normal Hb of 15 g/dl represents about a 7% reduction in the C_aO_2 and is easily tolerated by persons with a normal circulatory capacity. A S_aO_2 of 85% in normal arterial blood corresponds to a P_aO_2 of about 6.7 kPa (50 mmHg); the C_aO_2 is then about 12% lower than normal. The latter C_aO_2 reduction is also well tolerated by healthy persons, but may be dangerous in patients with cardiovascular dysfunction. The **tolerance to hypoxemia** depends on the **Hb** concentration, and on whether or not a **compensatory increase in cardiac output** can secure an adequate DO_2 (see Part 2-3).

The C_aO_2 at a given PO_2 varies, however, with factors like blood acidity, temperature, and others. In persons with severe acidosis, a P_aO_2 of 8 kPa (60 mmHg) that would be well tolerated under normal conditions could result in a disastrously low S_aO_2 in the 50-55% range (fig. 4-12). The same P_aO_2 in a person with a substantially left-shifted HbO_2 curve (e.g. with a pH 7.70, Tp 27°C, or fetal Hb – see Part 2-3) may correspond to a S_aO_2 of 95%, i.e. a C_aO_2 close to normal. From an O_2 delivery to the tissues (DO_2) perspective, the level of S_aO_2 is thus the more logical way to define hypoxemia. From a pulmonary function perspective, the levels of P_aO_2, when compared to the calculated P_AO_2, are good indicators of the gas exchange conditions of the lungs. P_aO_2 is used in the common definition of respiratory failure as well as in diagnosis of ARDS and classification of its severity (see below) In this compendium, hypoxemia is defined as a P_aO_2 < 8 kPa (60 mmHg) *and/or* a S_aO_2 < 91%.

Hypercarbia: definitions and significance.

To be excreted from the venous blood, the CO_2 must be able to diffuse from the blood into the alveolar gas. The efficiency of such diffusion is determined by the difference in gas pressure (i.e. the P_VCO_2 *vs* the P_ACO_2 gradient). If the ventilation of perfused alveoli is reduced and the P_ACO_2 increases, the pressure difference may become too low for efficient diffusion and the blood leaves the lungs with increased PCO_2. A *rise* in P_VCO_2 (increased production or reduced flow) *or a decrease* in P_ACO_2 (increased ventilation) augments the gradient, favoring increased diffusion.

Hypercarbia (also called **hypercapnia**) denotes an increased PCO_2 level in the arterial blood. There is widespread consensus about **defining hypercarbia as a P_aCO_2 > 6 kPa (45 mmHg)** (93), levels **above 10 kPa** (75 mmHg) are often called ***severe*** **hypercarbia**. A change in PCO_2 may not always reflect a change in the total CO_2 content of the blood (see Part 2-3). Acute hypercarbia causes respiratory acidosis (Part 5-2), levels below 10-12 kPa (75-90 mmHg) are otherwise well tolerated as long as an increased F_iO_2 can keep the P_AO_2 (and thus the P_aO_2) at acceptable levels. The rightward shift of the HbO_2 curve during respiratory acidosis requires a higher P_aO_2 to maintain a satisfactory S_aO_2.

Reduced alveolar ventilation as a cause of hypoxemia and/or hypercarbia.

Hypoxemia and hypercarbia can occur simultaneously or separately, severe hypercarbia is *always* accompanied by hypoxemia if no supplemental O_2 is given. When breathing normal air at sea level, **hypoxemia** may be a result of

i) **Generalized hypoventilation** with essentially normal alveolar-capillary function *and/or*
ii) **An increase in regions where perfused alveoli** are **hypo-** or **non-ventilated.**

Hypoxemia may, however, also occur in persons with perfectly healthy lungs and normal ventilation volumes when the P_AO_2 is low (see below) or the Hb is dysfunctional (low S_aO_2, Part 2-3).

Hypercarbia may be a result of

i) **Generalized hypoventilation** and/or

ii) **An increased in regions where ventilated alveoli are hypo- or non-perfused.**

CONDITIONS ASSOCIATED WITH HYPOXEMIA: AN OVERVIEW

Hypoxemia in persons with normal airways and alveolar-capillary units.

In persons with **normal** or **increased ventilation volumes,** hypoxemia may be the result of

- **Reduced ambient pressure** (and thus low inspired PO_2) at high altitudes.
- **Reduced F_iO_2 in the ambient gas** (e.g. when O_2 is partially displaced by other gases, inhalation of asphyxiating gases).
- **Rapid release of a "second gas"** from the blood to alveoli (see Part 4-1).

In persons with **decreased ventilation volumes,** hypoxemia may be the result of failure of the inspired gas to add enough fresh O_2 molecules to the FRC to maintain a normal P_AO_2. In such conditions, an increase in alveolar and arterial PCO_2 accompanies the hypoxemia. In **hypoventilating** individuals, the reduced alveolar ventilation cannot maintain excretion of normal amounts of CO_2 without increasing the alveolar (and thus also the arterial) CO_2 concentration. The PO_2 and PCO_2 then change in opposite directions; the sum of the pressure of gases in the alveoli at end inspiration and – expiration must be equal to the ambient pressure. During hypoxemia due to *reduced ambient pressure*, *reduced F_iO_2,* or *hypoventilation*, the calculated $\mathbf{P_AO_2}$ and the measured $\mathbf{P_aO_2}$ will be close to equal. Common causes of the latter are reduced activity of the respiratory muscles *or* upper airway obstruction *or* both.

Hypoxemia due to dysfunctional alveolar-capillary units.

In individuals breathing *room air* at sea level, with *normal or increased ventilation volumes*, **hypoxemia** occurs when an increased fraction of the pulmonary blood flow passes through

- **Regions with non-ventilated alveoli**, i.e. V/Q ratios = 0 = **shunt**, see below *or*
- **Regions with hypoventilated alveoli**, i.e. very **low V/Q ratios**.

In either type of dysfunction, the measured P_aO_2 is substantially lower than the P_AO_2 calculated by the alveolar gas equation. The response to increased F_iO_2 is, however, different (Part 4-4).

HYPOXEMIA WITH NORMAL GAS EXCHANGE FUNCTION: DETAILS, AND CALCULATION OF THE P_AO_2

The consequences of changes in ambient pressure (see table 4-1 below).

Changes in the atmospheric (barometric) pressure as a result of high altitudes (low ambient pressures) or during diving (high ambient pressures) also change the P_AO_2 in lungs with normal gas exchange function. Calculation of the P_AO_2 on top of **Mount Everest** (where the meanP_B is $\approx$ 33.7 kPa *or* 253 mmHg), utilizing the alveolar air equation and *assuming* a normal P_ACO_2, indicates that survival without supplemental O_2 should be impossible if the P_ACO_2 is normal $\mathbf{P_AO_2}$ $\approx [(33.7 - 6.3) \times 0.209] - 5.3/0.8 \approx$ **- 0.9 kPa** *or* $[(253 - 47) \times 0.209] - 40/0.8 \approx$ - 7 mmHg.

As a negative value for P_AO_2 is not possible, such calculations illustrates the limitation of using this equation for conditions where one of the factors is assumed and not actually measured.

Altitude		PO_2 if F_iO_2=0.21				PO_2 if F_iO_2=0.30				PO_2 if F_iO_2=0.50				PO_2 if F_iO_2=0.70				PO_2 if F_iO_2=1.0			
		Ambient air		Alveolar gas		Ambient air		Alveolar gas		Ambient air		Alveolar gas		Ambient air		Alveolar gas		Ambient air		Alveolar gas	
Meters	*Feet*	kPa	*mmHg*	kPa	*mmHg*	kPa	*mmHg*	kPa	*mmHg*	kPa	*mmHg*	kPa	*mmHg*	kPa	*mmHg*	kPa	*mmHg*	kPa	mmHg	kPa	*mmHg*
0	*0*	21,2	*159*	13,2	*99*	30,4	*228*	21,8	*163*	50,7	*380*	40,7	*305*	70,9	*532*	59,6	*447*	101,3	760,0	88,0	*660*
500	*1 690*	20,0	*150*	12,0	*90*	28,7	*215*	20,0	*150*	47,8	*359*	37,8	*284*	66,9	*502*	55,6	*417*	95,6	717,2	82,3	*617*
1 000	*3 381*	18,8	*141*	10,8	*81*	27,0	*203*	18,4	*138*	45,0	*338*	35,1	*263*	63,1	*473*	51,7	*388*	90,1	675,9	76,8	*576*
1 500	*5 071*	17,8	*133*	9,7	*73*	25,5	*191*	16,9	*127*	42,5	*319*	32,5	*244*	59,5	*447*	48,2	*362*	85,0	638,0	71,7	*538*
2 000	*6 762*	16,7	*125*	8,7	*65*	23,9	*180*	15,3	*115*	39,9	*299*	29,9	*224*	55,9	*419*	44,5	*334*	79,8	598,7	66,5	*499*
2 500	*8 452*	15,7	*118*	7,7	*58*	22,6	*170*	14,0	*105*	37,7	*283*	27,7	*208*	52,7	*396*	41,4	*311*	75,3	565,1	62,0	*465*
3 000	*10 143*	14,8	*111*	6,9	*51*	21,2	*159*	12,7	*95*	35,3	*265*	25,4	*191*	49,4	*371*	38,2	*287*	70,6	529,6	57,4	*430*
3 500	*11 833*	13,9	*104*	7,1	*54*	20,0	*150*	12,6	*94*	33,3	*250*	24,6	*184*	46,6	*350*	36,6	*274*	66,6	499,8	54,5	*409*
4 000	*13 523*	13,0	*98*	6,7	*51*	18,7	*140*	11,8	*88*	31,1	*234*	22,9	*172*	43,6	*327*	34,0	*255*	62,3	467,2	50,7	*380*
4 500	*15 214*	12,3	*92*	6,5	*49*	17,6	*132*	11,3	*84*	29,4	*221*	21,7	*163*	41,1	*309*	32,1	*241*	58,8	441,0	47,7	*358*
5 000	*16 904*	11,5	*86*	6,1	*46*	16,5	*124*	10,5	*79*	27,5	*206*	20,2	*151*	38,5	*289*	29,8	*224*	55,0	413,0	44,3	*333*
5 500	*18 595*	10,9	*82*	5,7	*43*	15,6	*117*	9,8	*74*	26,0	*195*	18,9	*142*	36,4	*273*	27,9	*210*	52,0	390,0	41,5	*311*
6 000	*20 285*	10,0	*75*	5,1	*38*	14,4	*108*	8,9	*67*	24,0	*180*	17,1	*128*	33,6	*252*	25,4	*190*	48,0	359,8	37,8	*283*
6 500	*21 975*	9,5	*71*	4,7	*35*	13,6	*102*	8,2	*61*	22,6	*170*	15,9	*119*	31,7	*238*	23,6	*177*	45,3	339,6	35,2	*264*
7 000	*23 666*	8,8	*66*	4,4	*33*	12,6	*94*	7,6	*57*	21,0	*157*	14,6	*110*	29,4	*220*	21,7	*163*	41,9	314,6	32,2	*242*
7 500	*25 356*	8,3	*62*	4,4	*33*	11,9	*89*	7,4	*55*	19,8	*149*	13,9	*105*	27,7	*208*	20,5	*154*	39,6	297,0	30,4	*228*
8 000	*27 047*	7,8	*59*	4,3	*32*	11,2	*84*	7,1	*53*	18,7	*140*	13,2	*99*	26,2	*196*	19,4	*145*	37,4	280,6	28,6	*214*
8 500	*28 737*	7,4	*55*	4,0	*30*	10,6	*80*	6,6	*49*	17,7	*133*	12,3	*92*	24,7	*186*	18,1	*135*	35,3	265,2	26,6	*200*
9 000	*30 428*	7,0	*52*	3,7	*28*	10,0	*75*	6,1	*46*	16,7	*125*	11,5	*86*	23,4	*176*	16,8	*126*	33,4	250,8	24,9	*186*
9 500	*32 118*	6,4	*48*	3,1	*23*	9,2	*69*	5,3	*40*	15,3	*114*	10,0	*75*	21,4	*160*	14,8	*111*	30,5	228,9	21,9	*165*
10 000	*33 808*	5,7	*43*	2,4	*18*	8,1	*61*	4,3	*32*	13,6	*102*	8,3	*63*	19,0	*142*	12,4	*93*	27,1	203,5	18,5	*139*
11 000	*37 189*	4,8	*36*	1,5	*11*	6,8	*51*	3,0	*22*	11,4	*86*	6,2	*46*	16,0	*120*	9,4	*71*	22,8	171,2	14,2	*107*

P_AO_2 in the normal range | P_AO_2 corresponding to S_aO_2 < 90% in normal blood. | Ambient air = estimated barometric pressure.

Alveolar gas pressures calculated utilizing the alveolar gas equation.
At elevations above 2 500 m, approximate corrections are made for assumed reduction of ambient temperature and hypoxemic hyperventilation.

Table 4-1. *PO_2 in ambient air and alveolar gas as a function of elevation above sea level.*

In persons with normal function of the respiratory system, hypoxemia leads to hyperventilation. Some degree of hyperventilation starts at a S_aO_2 of 90%; it increases linearly with decreasing S_aO_2 (but hyperbolic with decreasing P_aO_2) and reaches a minute ventilation volume of approximately 35 l/min at S_aO_2 values around 70% (94). Based on measurements in persons acclimatized to extreme altitudes, the ventilation increase (and thus reductions in P_ACO_2) accelerate when calculated P_AO_2 is reduced to 5.3-4.7 kPa (40-35 mmHg) (95). The actual ventilation response differs substantially, however, between individuals. The ventilation response to acute and chronic hypoxemia is also different; a fast reduction in blood and tissue PCO_2 creates a respiratory inhibition mediated by the central chemoreceptors.

When *measured* PCO_2 values are inserted in the equation, the calculated P_aO_2 becomes closer to actual values. If the P_ACO_2 is reduced to 1.0 kPa (7.5 mmHg), as calculated from gas expired at the summit of Mt Everest (96), calculations using the alveolar air equation becomes

P_AO_2 ≈ [(33.7 – 6.3) × 0.209] – 1/0.8 ≈ **4.5 kPa** *or* [(253 – 47) × 0.209] – 7.5/0.8 ≈ **33.3 mmHg.**

If P_ACO_2 is reduced to 1.8 kPa (13.3 mmHg), the mean value measured in arterial blood of mountain climbers 400 m below the Mt Everest summit (97), the equation becomes

P_AO_2 ≈ [(33.7 – 6.3) × 0.209] – 1.8/0.8 ≈ **3.48 kPa** *or* [(253 – 47) × 0.209] – 13.3/0.8 ≈ **26.4 mmHg.**

The P_aO_2 could not be measured directly but the median value, calculated from the measured S_aO_2 values and corrected for pertinent factors, was **4.0 kPa** (**30 mmHg**).

During **diving** at a depth of about **10 meters**, the gas pressures in the airways and body fluids are *twice* those at sea level, i.e. 202.6 kPa *or* 1520 mmHg. When breathing compressed air at this depth, the alveolar PO_2 can be calculated to

P_AO_2 = [(202.6 – 6.3) × 0.209] – 5.3/0.8 ≈ **34.4 kPa** *or* [(1520 – 47) × 0.209] – 40/0.8 ≈ **258 mmHg**, i.e. about 2.5 times higher than at sea level.

A normal P_AO_2 (and P_aO_2) at a depth of 10 meters would be obtained by breathing a gas containing about 10% O_2

P_AO_2 = [(202.6 – 6.3) × 0.1] – 5.3/0.8 ≈ **13.0 kPa** *or* [(1520 – 47) × 0.1] – 40/0.8 ≈ **98 mmHg.**

The tolerance of healthy persons to hypoxemia resulting from acute reductions in F_iO_2 at normal ambient pressure.

Breathing gas where the O_2 in the air has been partially displaced by other gases reduces the P_AO_2 and thus the P_aO_2. Healthy volunteers acutely exposed to inspiratory gas containing 10.5 % O_2 (half the normal F_iO_2, and similar to the concentration of alveolar O_2 molecules in the ambient air at an altitude of around 5 500 – 6 000 meters, see table 4-1) hyperventilated to a P_aCO_2 of 3.5 kPa (27 mmHg) (98), which makes room for more O_2 in the alveolar air. The P_AO_2, calculated according to the alveolar air equation, should be

P_AO_2 = [(101.3 – 6.3) × 0.105] – 3.5/0.8 ≈ **5.6 kPa** or **43 mmHg**.

The mean P_aO_2 actually measured in the test persons was **6.3 kPa**. An acute respiratory alkalosis in the blood of test persons, with a pH of about 7.52 and a leftward shift of the HbO_2 curve would then result in a **S_aO_2** of around **85%**.

At sea level, a 50% reduction of O_2 in the inspired gas (i.e. to ≈10% O_2, F_iO_2 0.1) may represent the lowest acceptable level for healthy persons with normal Hb concentrations. In a study of both humans and dogs, excess lactate production was found after 20 minutes when F_iO_2 was lower than 0.1 (99). Even lower O_2 concentrations may be tolerated for a limited time; acute

exposure of young healthy volunteers to inspiratory O_2 concentrations as low as 7% O_2 for more than 15 min was tolerated without apparent ill effects when the PCO_2 was kept constant to avoid changes in blood pH and thus in the HbO_2 dissociation curve (100). The resulting mean P_aO_2 was **4.6 kPa** (34.6 mmHg). In experimental animals (rats) with high metabolic rates, however, breathing 10% O_2 for 2 hours proved lethal to most animals (101), illustrating the importance of both species differences and time of exposure in research.

The data above illustrate the considerable capacity of resting *healthy organisms* to tolerate reductions of O_2 in the inspired air, and thus a substanstially reduction of P_aO_2. Such acute decreases in PO_2 levels *cannot be expected to be tolerated by persons with severe anemia, or with any condition that reduces the reserve capacity of the circulatory system.*

Acute hypo- or hyperventilation with essentially normal alveolar-capillary function: the connection between P_ACO_2 and P_AO_2.

In persons with normal lungs, breathing normal air, **alveolar hypoventilation** results in **hypoxemia** and **high CO_2 in the alveoli and blood;** a substantial increase in P_aCO_2 corresponds to a reduction in the P_aO_2, expressed in kPa, by *roughly* the same magnitude (more precisely $P_aCO_2 \times 1.2$, according to the alveolar gas equation). Hypoventilation that results in a P_ACO_2 of 12.5 kPa (94 mmHg) is accompanied by a P_AO level of 4.3 kPa (32 mmHg) when breathing normal air. The *effect of hypoventilation on* P_AO_2 can be fully compensated for by administering supplementary O_2 to the inspired air (fig. 4-13); a F_iO_2 of 0.3 will normalize the P_AO_2 in a person with normal lungs hypoventilating to a $P_ACO \approx 12.5$ kPa (see other calculation examples below).

Smaller tidal- and minute volumes require an increased concentration of CO_2 in the expired gas (and thus in the alveolar CO_2) to excrete an amount of CO_2 equal to that generated by the tissues (fig. 4-13). High P_aCO_2 levels due to severe hypoventilation are, *per se*, seldom a direct cause of death if the F_iO_2 is increased appropriately. Even very high PCO_2 levels can be tolerated; in one case report, a P_aCO_2 of 35.3 kPa (265 mmHg) with a pH of 6.65, building up over 3.5 hours (102)) proved to be compatible with survival and an uneventful recovery as the P_aO_2 was maintained at satisfactory levels by increased F_iO_2 during the whole period.

The most common cause of acute *out-of-hospital* hypoxemia and increased P_aCO_2 is respiratory depression due to *drug abuse* (primarily opiates, but intoxications with many other drugs also depress ventilation); major *damage to the central nervous system* or the *spinal cord* may also cause acute respiratory insufficiency. Acute attenuation or loss of muscle strength by *neuromuscular blocking agents* occurs almost exclusively *within hospitals*; incomplete reversal of such agents after general anesthesia may be disastrous if unrecognized (see also Part 4-3 for details). Hypoventilation after traumatic damage to the thoracic cage (pain and instability) or diaphragm is often accompanied by damage to the pulmonary tissue, which aggravates the hypoxemia.

The effect of hypo- and hyperventilation on P_ACO_2 and P_AO_2: calculations.

If a hypoventilating person breathing **room air** has a **P_aCO_2 of 10 kPa** (75 mmHg), the **P_AO_2** calculated using the alveolar gas equation is

$[(101.3 - 6.3)\ \text{kPa} \times 0.209] - 10/0.8 \approx$ **7.4 kPa** *or* $[(760 - 47)\ \text{mmHg} \times 0.209] - 75/0.8 \approx$ **55 mmHg.**

As such an acute CO_2 increase results in respiratory acidosis with a **pH** of around **7.20**, this PO_2 then corresponds to a **S_aO_2** around **80%**. If the patient's S_pO_2 was monitored, interventions to increase ventilation (or the F_iO_2) would hopefully have been instituted long before this level was reached. In this calculation example and those below, the effect of *development of atelectasis*

that often accompanies small ventilation volumes in supine persons is ignored; the P_aO_2 values in such patients are will therefore often be *lower* than those calculated (see shunting below).

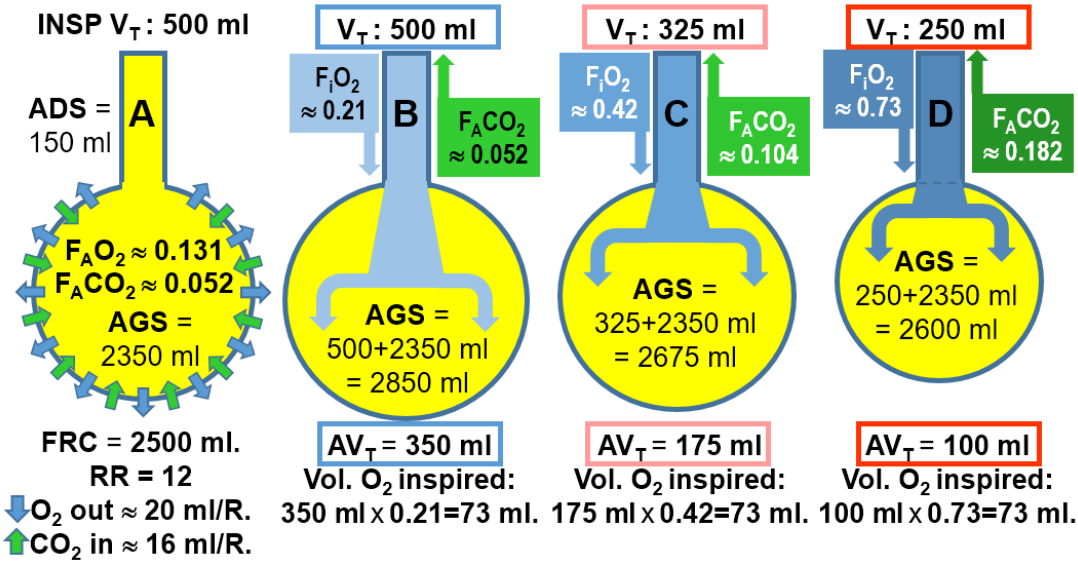

Figure 4-13. *Effect of homogenous hypoventilation of the alveolar gas space* **(AGS)**, *the relationship between inspired* **(V_T)** *and alveolar tidal volumes* **(AV_T)** *tidal volumes, and the increase in* **F_iO_2** *necessary to compensate for the reduced ventilation.* **A** *represents a normal steady state, here set as a* **FRC** *of 2 500 ml (anatomical dead space* (**ADS**) *of 150 ml + AGS 2350 ml) and normal fractions* **(F_A)** *of* **O_2** *and* **CO_2** *in the alveolar gas. Volumes* **out** *and* **in** *represent the volume of gases exchanged between blood and alveolar gas for each breath* **(R).**
B. *As* **A**, *at end inspiration of a V_T of 500 ml.* **C**. *If the V_T is reduced to 375 ml (by 30%), the alveolar tidal volume is 50% of normal. The inspired F_iO_2 must double to supply the same number of O_2 molecules to the alveoli with each breath.* **D**. *If the V_T is reduced to 250 ml (by 50%), the alveolar ventilation is reduced to about 30 % of normal; the inspired F_iO_2 must increase to above 0.7 to maintain the same alveolar supply of O_2 per breath.*
Effect on CO_2: *The alveolar CO_2 fraction* (**F_ACO_2**), *and thus also the* **P_aCO_2**, *must increase by about 100% and 250%* in **C** *and* **D**, *respectively, to excrete the same amount of CO_2 from the body as before. White numbers indicate the calculated fraction of CO_2* (**F_ACO_2**) *in alveolar air corresponding to the reduced V_T.*

On the other hand, **hyperventilation when breathing room air** (e.g. in severe metabolic acidosis, fear, or other psychological mechanisms) leading to a **P_ACO_2 decrease** to **2.5 kPa** will increase the alveolar PO_2 substantially; approximate **P_AO_2** is then

$[(101.3 - 6.3)\ kPa \times 0.209] - 2.5/0.8 \approx$ **16.7 kPa** *or* $[(760 - 47)\ mmHg \times 0.209] - 19/0.8 \approx$ **126 mmHg.**

If supplementary oxygen, resulting in a **F_iO_2 = 0.4,** is administered to a patient with normal ventilation volumes and **normal P_aCO_2**, the calculated **P_AO_2 at sea level** will be

$[(101.3 - 6.3)\ kPa \times 0.4] - 5.3/0.8 \approx$ **31.4 kPa** *or* $[(760 - 47)\ mmHg \times 0.4] - 40/0.8 \approx$ **235 mHg**.

If the ventilation wanes and **P_aCO_2 rises to 20 kPa** (150 mmHg) within a few hours while still breathing gas with **F_iO_2 = 0.4**, **P_AO_2 can still be in the normal range**, provided that atelectasis are avoided and the gas exchange in most alveolar-capillary units remains normal

$[(101.3 - 6.3)\ kPa \times 0.4] - 20/0.8 \approx$ **13.0 kPa,** *or* $[(760 - 47)\ mmHg \times 0.4] - 150/0.8 \approx$ **98 mHg**.

The accompanying respiratory acidosis results in a pH of around 7.10, which decreases the HbO_2 affinity and causes a substantial rightward shift of the dissociation curve. Even then, the reduc-

tion of S_aO_2 will be relatively mild, to about 90-91% (see Part 2-3). In this case, the acute CO_2 increase results in a S_pO_2 level that in most patients would not be considered to be a cause of great concern, and a potentially dangerous respiratory acidosis combined with increased atelectasis formation may remain undetected.

Thus, in patients to whom supplementary O_2 is administered, **oxygen saturation** as monitored with a pulse oximeter may be normal despite the development of **severe respiratory acidosis** (fig. 4-12). If the patient receives anti-atelectatic treatment (e.g. intermittent deep breathing, increased airway pressures, etc., see Part 4-4), the formation of atelectasis associated with hypoventilation can be avoided and S_pO_2 stay normal.

RIGHT-TO-LEFT SHUNTING OF VENOUS BLOOD OUTSIDE OR INSIDE THE LUNGS LEADS TO HYPOXEMIA

Central cardiovascular shunts (extra-pulmonary shunts).

If part of the returning venous blood passes *directly* to the arterial side without passing through the lungs (e.g. from the right side of the heart to the left as in some patients with atrium septum defects (103) or other congenital cardiac and/or vascular diseases (104)) (see also Part 3-2), the arterial blood exiting from the left ventricle is a mixture of

- **Mixed venous blood,** where the O_2 content ($\mathbf{C_VO_2}$) is determined by the ratio between O_2 delivery and consumption (the $DO_2/\dot{V}O_2$ ratio), *and*
- **Blood that has been equilibrated with alveolar gas** during passage through the lungs (transpulmonary blood flow – **TB**).

Some of the blood passing through the normal bronchial circulation represents such a right-to-left shunt; it represents only a few percent of the total flow and has little effect on the total oxygenation of the blood.

The shunt fraction (SF).

The fraction of the total blood flow that *does not* pass through the lungs (i.e. mixed venous blood), relative to the total blood flow (i.e. the C.O.), is the **shunt fraction** (fig. 4-14). The magnitude of this fraction determines the impact of such a shunt on the O_2 content of the arterial blood, i.e. P_aO_2 and S_aO_2. The size of the shunt fraction can be calculated using Berggren's equation (see below for calculation and limitations), using three parameters:

- The $\mathbf{C_VO_2}$, which is calculated from the PO_2, SO_2, and Hb *measured* in mixed venous blood,
- The $\mathbf{C_aO_2}$, which is calculated from the PO_2, SO_2, and Hb *measured* in the arterial blood**.**
- The *calculated* **O_2 content of the trans-pulmonary blood,** i.e. blood that has passed through the lungs ($\mathbf{C_{TB}O_2}$). Contrary to the other two parameters, where PO_2, SO_2 and Hb are measured directly, calculation of this parameter rest on the *assumption* that the gas exchange in the lungs is normal, i.e. the PO_2 of the trans-pulmonary blood flow is close to *equal* to the P_AO_2 as calculated by the alveolar air equation. For such calculation, the precise F_iO_2 must be known; the corresponding SO_2 is then calculated after correcting for pH, temperature, and P_aCO_2.

In persons with normal lung function, accurate calculations of the shunt fraction can then be carried out. Arterial blood can be obtained from any artery; mixed venous blood must be obtained from the deep part of the right ventricle or the pulmonary artery. If the assumption about normal gas exchange in the lungs does not hold true, calculation of the $C_{TB}O_2$, and thus the shunt fraction, will be inaccurate.

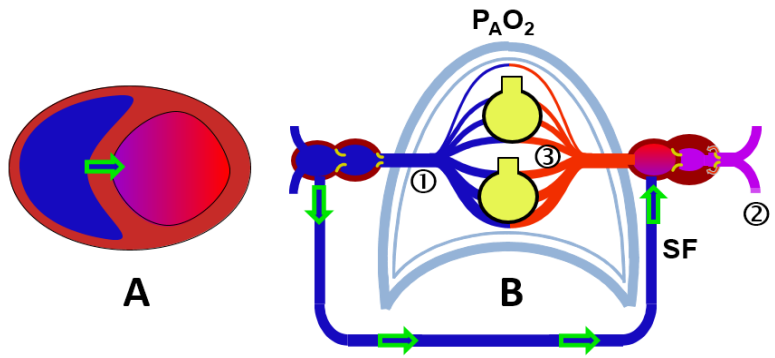

Figure 4-14. *Depictions of the principle of of a cardiovascular shunt.* **A:** *A defect in the atrial septum (see Part 3-2) combined with increased diastolic pressures may create a right-to-left diastolic flow of venous blood that mixes with the blood that has passed through the lungs.* **B:** *The effect on arterial PO_2 is the same as if a portion of the blood is shunted directly from the venous side to the left atrium through aberrant vessels without passing through the lungs.* **SF:** *shunt fraction,* **①: C_VO_2, ②: C_aO_2, ③ TB**. *See text for calculations.*

For **simplified bedside calculation** purposes in individuals without severe anemia and with normal lung function, we can assume that the blood O_2 content is proportional to its SO_2. The amount of dissolved O_2 (PO_2) normally represents only 1.5-2% of the O_2 in the blood (see Part 2-3), ignoring it creates only a minuscule error. If we assume that the blood passing through the lungs (transpulmonary blood – **TB**) has a normal SO_2 of 97.5% when entering the pulmonary veins, and that the SO_2 of the mixed venous blood is 65%, the weighted mean S_aO_2 with a **shunt fraction (SF) of 0.25** (i.e. ¼ of the total flow is shunted outside the lungs) results in

S_aO_2 ≈ **TB** (97.5% x ¾) + **SF** (65% x ¼) = 73% + 16% = **89%**, which is close to a

P_aO_2 of **7.5 kPa** (56 mmHg) if the HbO_2 curve has a normal position.

Similarly, assuming a **shunt fraction of 0.5** and using the same values as above results in

S_aO_2 ≈ TB (97.5 x ½) + SF (65 x ½) = 49 + 32 = **81%** (which is close to a **P_aO_2** of **6.0 kPa** (45 mmHg) with a normal HbO_2 curve.

The numbers used in the above calculations are chosen for illustrative purposes; in clinical reality, the S_VO_2 would be reduced further when the S_aO_2 decreases until a new balance is reached. The C_VO_2 can be calculated by means of a re-arranged Fick's equation and solving it for C_VO_2, i.e. $[C_aO_2 \times C.O. - \dot{V}O_2] = C_VO_2 \times C.O.$ *or* **$C_VO_2 = C_aO_2 - \dot{V}O_2/C.O.$** The S_VO_2 can be calculated accurately by substituting C_VO_2 and C_aO_2 with all terms in the O_2 content equation, or using a simplification *without* the PO_2 contribution where both sides of the equation above is divided by 1.34 x Hb (see Part 2-3).

Intrapulmonary shunts.

The resulting change in arterial O_2 content will be the same as those calculated above if a fraction of the mixed venous blood flows through *lung areas where no gas exchange takes place* (e.g. atelectasis, areas with occluded airways or fluid-filled alveoli – see below). The V/Q ratio in such areas is zero, and the blood flow through such vessels represents an **intrapulmonary shunt** (fig. 4-14, B). If the rest of the pulmonary blood flow passes through alveolar areas where it is oxygenated in the normal manner (i.e. $P_aO_2 \approx P_AO_2$), the consequences of such shunting for the arterial blood O_2 content can be calculated analogous to that of cardiovascular shunts above (see below for calculation examples). If the fraction of the blood that passes areas with normal alveoli attains the same PO_2 as that calculated by the alveolar gas equation, any increase in pulmonary shunt augments the difference between the calculated P_AO_2 and the measured P_aO_2 (the alveolar-arterial (A-a) difference or -gradient).

Common causes of intrapulmonary shunting.

Shunting occurs when a fraction of the pulmonary blood flow traverses lung areas with

- **Fluid-filled alveoli.** Alveoli that are filled with fluid (e.g. edema fluid, secretions, aspirated material, pus, *or* blood) do not participate in gas exchange and do not supply additional O_2 to the perfusing blood.
- **Non-ventilated alveoli.** In areas located distal to a total airway occlusion, the perfusing blood rapidly takes up most of the O_2 in the alveolar gas. Within minutes, the PO_2 of the gas of such alveoli becomes equilibrated with that in the mixed venous blood PO_2. After this happens, there is no further diffusion of O_2 from alveoli to capillaries and the blood perfusing such alveolar areas becomes a shunt flow.
- **Atelectatic alveoli.** If a total airway occlusion persists, *all* the gas within these alveoli gradually becomes absorbed due to the sub-atmospheric gas pressure in venous blood, i.e. the sum of gas pressures in venous blood is smaller than in the alveolar air. Such alveoli gradually collapses and becomes atelectasis. When this occurs, no O_2 enters the perfusing capillaries. Atelectasis may also occur as a consequence of external pressure on the lungs (e.g. pneumothorax, pleura effusions, hemothorax) – or simply the weight of edematous lung tissue above the lowest part of the lungs. Re-expanding larger atelectatic areas may lead to a dramatic improvement in arterial oxygenation.

Even severely hypoventilated alveoli (i.e. a very low V/Q) add *some* new O_2 molecules to the passing blood; such alveolar areas do *not* represent a *true shunt* but nonetheless have similar properties when it comes to the effect of increased F_iO_2 (see below, also Part 4-4).

The level of hypoxemia resulting from intrapulmonary shunts.

The impact of pulmonary shunts on the O_2 content of arterial blood is mainly determined by

- **The shunt fraction**, i.e. the relative percentage of mixed venous blood that mixes with blood from ventilated and perfused parts of the lungs (see below for calculations).
- **The O_2 content of the mixed venous blood**, i.e. the relationship between DO_2 and VO_2, where both C.O. and Hb levels play an important role (see below).
- **Changes in the F_iO_2**, which influence the P_AO_2 and thus the O_2 content of the gas in alveoli that are still both ventilated and perfused. Increasing the F_iO_2 as a sole intervention has a modest effect on the P_aO_2 if the lungs consist of *either* areas representing a pure shunt *or* normally ventilated areas (see below). As the inspired air do not reach the alveolar space in fluid-filled, collapsed, or occluded (true shunt) alveolar areas, increasing the F_iO_2 has an effect only in the blood perfusing normally ventilated alveolar areas ((A) in fig. 4-15).

The **final effect** *of pulmonary shunts* and very low V/Q ratios on P_aO_2 is modified by the hypoxic pulmonary vasoconstriction (see below).

The local hypoxic pulmonary vasoconstriction (HPV).

Reduced alveolar PO_2 leads to local vasoconstriction of the pre-alveolar vessels. This mechanism reduces the capillary blood flow through shunt- and low V/Q areas, and redirects most of the pulmonary blood flow to areas with normal V/Q conditions (see below), thus ameliorating the effect of pulmonary shunt and V/Q disturbances on arterial blood oxygenation. Its efficiency varies between individuals; the efficiency of this response determines the consequences of pulmonary shunt on the P_aO_2 (see fig. 4-15 and 4-16). The effect of this mechanism may be attenuated or abolished by high pressures in the pulmonary vessels (105), and by the effects of

various vasodilating drugs (106). The effect of such drugs on HPV differs, however, between various agents (107).

Estimating the effect of intrapulmonary shunts on arterial blood oxygenation: calculation examples.

If the P_AO_2 in the still ventilated alveolar areas already is in the normal range, the Hb in the blood passing these areas is almost fully saturated with O_2 (i.e. SO_2 97-98%). Increasing the F_iO_2 to 1.0 (and thus the P_AO_2 to a theoretical maximum of 80-90 kPa (600-675 mmHg) may result in an SO_2 of 100%, i.e. an increase in SO_2 of only 2.5%; the increase in the number of dissolved O_2 molecules is about twice as much. In most diseased lungs, however, there are also *hypoventilated* alveolar areas (i.e. low V/Q areas), where increased F_iO_2 may have a substantial effect on the P_aO_2 (see below).

Rough bedside calculations can illustrate the effect of the first three factors above on arterial oxygenation in a semi-quantitative way when an intrapulmonary shunt is present. The Hb is the same in all portions of the blood. If we, for the sake of simplification, ignore the small contributions of physically dissolved O_2 in the blood, the O_2 content in the blood exciting from areas (A), (B), and (C) in fig. 4-15 is roughly proportional to its HbO_2 saturation (see also above).

In the calculation examples below, **one-third** of the blood passing through the lungs represents a **shunt flow** with a **mixed venous** SO_2 and O_2 content, while the other two-thirds of the flow ((**A**)+(**B**) in fig. 4-16) are fully equilibrated with the alveolar gas. **When breathing room air** (F_iO_2 0.21) **at sea level (**PB 101.3 kPa), normal oxygenation of the blood exiting these alveolar areas can be assumed to have an SO_2 of around 97.5%. If the **SO_2 of mixed venous blood is 50%** (due to a reduced DO_2), the SO_2 of blood entering the left atrium is

SO_2 ≈ (97.5% x 2/3) + (50% x 1/3) ≈ **82%**, which at normal pH and temperature corresponds to a PO_2 of around **6.2 kPa** (46 mmHg).

Effect of increasing the F_iO_2 to 0.5 in patients with 33% shunt flow.

When breathing gas with a F_iO_2 of 0.5 (**P_AO_2 ≈ 40 kPa** or 300 mmHg) and the same S_VO_2 as above, the simplified equation becomes

SO_2 = (99.5% x 2/3) + (50% x 1/3) = **83%**, which at normal pH and temperature corresponds to a PO_2 of around **6.4 kPa** (48 mmHg). Increasing the F_iO_2 further to 1.0 has only minuscule effects on the P_aO_2 (see also Part 4-4: Therapy).

Effect of increasing the S_VO_2 in patients with a 0.33 shunt fraction.

If efforts to increase the DO_2 relative to the $\dot{V}O_2$ (e.g. hypothermia, increased Hb if low, increased C.O.) is successful, the **S_VO_2 will increase.** If S_VO_2 increases from 50% to 70% (by cooling and increasing the DO_2), calculations similar to those above for F_iO_2 0.21 yield

SO_2 = (97% x 2/3) + (70% x 1/3) = **88%**, which at normal pH and temperature corresponds to a PO_2 of around **7.3 kPa** (**55 mmHg**).

If breathing gas with a F_iO_2 of 0.5 (P_AO_2 ≈ 40 kPa or 300 mmHg) and the same S_VO_2, the equation becomes

SO_2 = 99.5% x 2/3 + 70% x 1/3 = **90%,** which at normal pH and temperature corresponds to a PO_2 of around **7.8 kPa** (**59 mmHg**). Again, increasing the F_iO_2 further to 1.0 has only minuscule effects on the P_aO_2 (see also fig 4-28 and 4-29).

The calculations above illustrate that in severe respiratory failure, where most of the gas exchange dysfunction is caused by pulmonary shunts or alveoli with a substantially reduced ventilation, increasing the DO_2 *relative to* the $\dot{V}O_2$ increases the P_aO_2, and more importantly, the C_aO_2, *more than* increasing the F_iO_2 above 0.5, see also Part 4-4: Therapy.

Limitations of calculation accuracy.

The calculations above are based on idealized "black-or-white" conditions, the calculated values may not reflect the more complex situation in pulmonary diseases. When edema is the cause of shunts, some areas will also be hypoventilated (low V/Q ratios – see below) due to interstitial

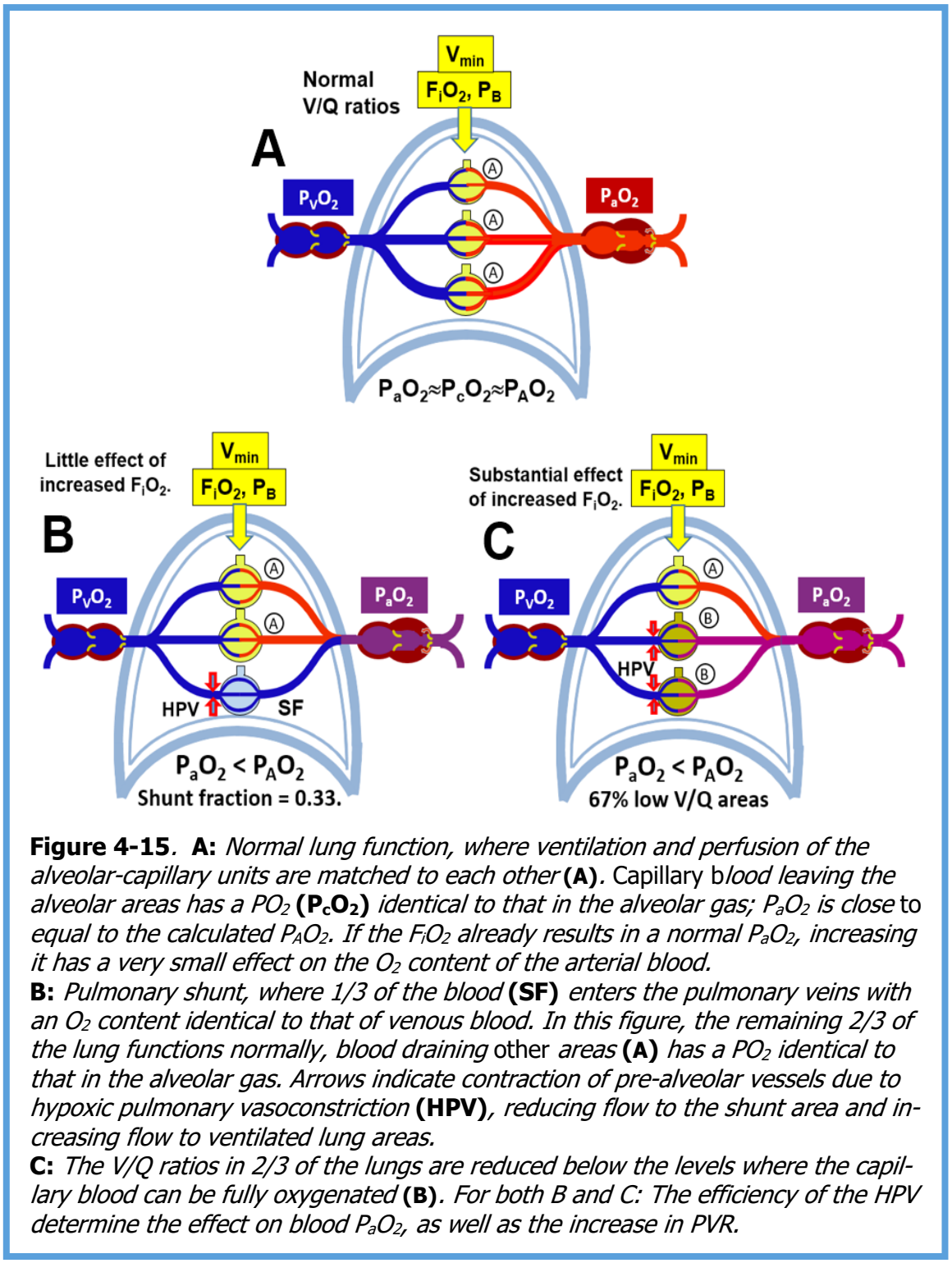

Figure 4-15. **A:** *Normal lung function, where ventilation and perfusion of the alveolar-capillary units are matched to each other* **(A)**. Capillary b*lood leaving the alveolar areas has a* PO_2 **(P_cO_2)** *identical to that in the alveolar gas;* P_aO_2 *is close* to *equal to the calculated* P_AO_2. *If the* F_iO_2 *already results in a normal* P_aO_2, *increasing it has a very small effect on the* O_2 *content of the arterial blood.*
B: *Pulmonary shunt, where 1/3 of the blood* **(SF)** *enters the pulmonary veins with an* O_2 *content identical to that of venous blood. In this figure, the remaining 2/3 of the lung functions normally, blood draining* other *areas* **(A)** *has a* PO_2 *identical to that in the alveolar gas. Arrows indicate contraction of pre-alveolar vessels due to hypoxic pulmonary vasoconstriction* **(HPV)**, *reducing flow to the shunt area and increasing flow to ventilated lung areas.*
C: *The V/Q ratios in 2/3 of the lungs are reduced below the levels where the capillary blood can be fully oxygenated* **(B)**. *For both B and C: The efficiency of the HPV determine the effect on blood* P_aO_2, *as well as the increase in PVR.*

edema, narrow airways, or localized compliance reductions. Total occlusion of a large airway will, on the other hand, result in a "true" shunt as the only cause of gas exchange dysfunction. Nevertheless, it can be concluded that

- In lungs where **shunting** *or* areas with **very low V/Q=0 ratios** are the main cause of blood oxygenation failure, increasing the **F_iO_2 has a limited effect** on the arterial PO_2 compared to the effect of interventions that increase the DO_2/ VO_2 ratio and thus the S_vO_2.
- The **effect** of **supplementary O_2** in the inspired air on the P_aO_2 indicate the prevalence of **true shunting** *vs* **low V/Q ratios** in diseased lungs.

The impact of pulmonary shunts on CO_2 excretion and arterial PCO_2.

The blood that passes through areas of the lungs where the V/Q = 0 excretes no CO_2 and leave the alveolar area with a PCO_2 equal to that in mixed venous blood. Despite this, the arterial levels of CO_2 often stay normal or subnormal during acute increases in shunt areas. Two factors contribute to this:

- If the tidal volume stays constant, and the shunt areas receive none of the inspired air, the volume of gas ventilating normally functioning alveolar space increases (see fig. 4-16). When their V/Q increases (i.e. V/Q > 1), more CO_2 is excreted from the ventilated alveolar space, and the blood leaving these areas has a lower CO_2 content than normal. This may compensate for the lack of CO_2 excretion in the shunt areas, giving the mixture of shunted and non-shunted blood a normal CO_2 level before leaving the left ventricle.
- Hypoxemia is a strong stimulus to increase ventilation; the response starts when the P_aO_2 falls below around 8 kPa (60 mmHg) and accelerates as the P_aO_2 falls further (108). As long as the force of the respiratory muscles stays intact, the ventilation volumes increase, and the ventilation of normally functioning alveoli increases.

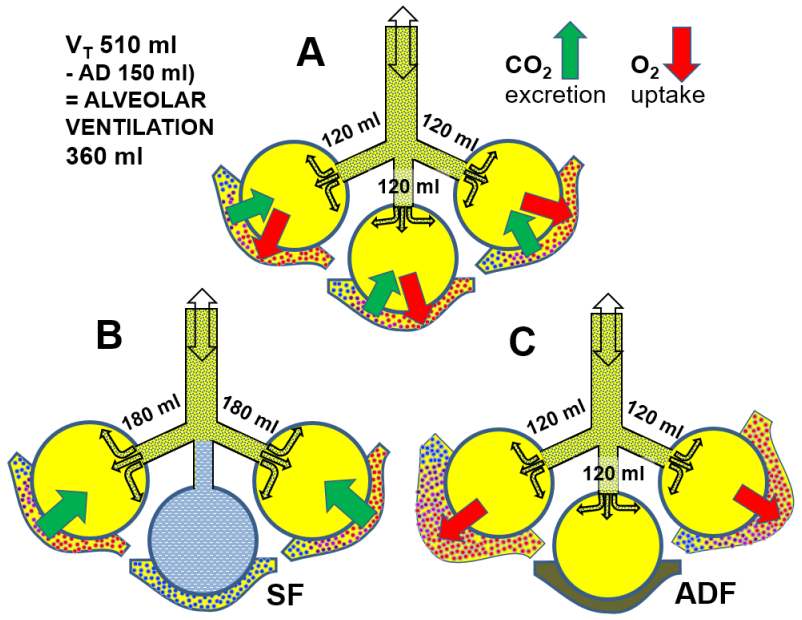

Figure 4-16. *Effect of intrapulmonary shunts and alveolar dead space on CO_2 excretion* (**B**) *and O_2 uptake* (**C**)*, respectively, compared to normal homogenous ventilation and perfusion* (**A**)*. Fluid filled alveoli* (**B**) *receive no ventilation, at constant tidal volumes, the other alveoli then receive increased ventilation volumes and can excrete more CO_2. In dead space* (**C**)*, non-perfused alveoli receive their normal share of ventilation; the perfused alveoli receive normal ventilation volumes. All the perfusing blood become equilibrated with PO_2 and PCO_2 in the alveolar gas.*

LOCALIZED HYPOVENTILATION AND HYPOXEMIA

(i.e. heterogeneously distributed alveolar areas with low V/Q ratios).

In most diseased lungs, not only pulmonary shunts but also areas with reduced V/Q ratios ($0 < V/Q < 1$) contribute to hypoxemia. In many such areas, the volume of fresh gas flowing into well-perfused alveoli is too small to supply the mass of O_2 necessary for bringing the O_2 saturation of the capillary blood in up to normal levels (fig. 4-15C). However, *some* new O_2–molecules are added to the alveolar air with each breath; the blood leaving such areas acquires an O_2 content that is somewhere *between* that of mixed venous blood and that of blood passing alveoli with normal ventilation. The end result depends on whether the mean V/Q ratio in dysfunctional areas is closer to 0 or 1. As an example, a reduction in the V/Q ratio to around 0.2 reduce the P_AO_2 to around 8 kPa (60 mmHg); at a ratio of around 0.5, the P_AO_2 increases to around 11 kPa (82 mmHg) while the CO_2 excretion is close to normal (83). In severe acute respiratory failure, V/Q ratios < 0.01 (or even closer to zero) which function essentially as shunts, may be the predominant change. On the other hand, alveoli with a V/Q ratio of 0.1 may have a PO_2 close to 6.5 kPa (49 mmHg), corresponding to an increase in pulmonary capillary blood SO_2 from that of normal venous blood by about 9%. In such alveoli, an increased F_iO_2 and thus the O_2 content in the alveolar air may result in a normal PO_2 in the blood leaving such areas.

A wide range of V/Q ratios may co-exist in the same lungs; the O_2 saturation of the blood leaving the various low-V/Q areas varies and the final S_aO_2 (and thus the P_aO_2) of the blood entering the left atrium represents a weighted mean of the contribution from all such areas (fig. 4-16). The most common causes of localized low V/Q conditions are

- **Reductions in airway dimensions and resistance** proximal to local alveolar areas, including intermittent airway collapse (see Part 4-1, closing volumes).
- **Localized reductions in compliance** of the lung tissue,

or any *combination* of the above.

Also in such conditions, the alveolar-arterial O_2 difference is increased, but not to the same extent as for a "true" shunt above. The two types show different responses to increased F_iO_2; even modest increases may have a substantial effect on the P_aO_2 if most of the pulmonary oxygenation problems are due to areas with low V/Q ratios (see below), while increasing the F_iO_2 to 1.0 has only modest effects on the arterial oxygenation if shunting is the predominant problem.

The expected effect of increasing the F_iO_2 in low V/Q areas.

If the amount of inspired air entering hypoventilated alveolar areas with each inspiration is about 50% of that necessary to saturate the Hb fully with O_2, increasing the F_iO_2 from 0.21 to 0.35 doubles the O_2 content of the inspired air, according to the alveolar gas equation. The alveolar PO_2 will then be in the normal range, the O_2 content in the blood leaving such areas will also be normal. If alveolar areas with such reduced V/Q ratios are the predominant cause of the oxygenation problems, giving supplementary O_2 by a nasal catheter or an open face mask (see also Part 4-4) can therefore result in a relatively normal O_2 content of the arterial blood. The difference between the *calculated* P_AO_2 and the *measured* P_aO_2 reveals, however, a significant V/Q disturbance.

The expected effect of manipulating C.O. and S_vO_2 on P_aO_2 in lungs with intrapulmonary shunt and very low V/Q fractions.

Having passed through a lung with V/Q disturbances, the oxygen content of the blood leaving this lungs is a mixture of adequately oxygenated, poorly oxygenated, and mixed venous blood (fig. 4-17). In patients with such lungs, the P_aO_2 and S_aO_2 vary with the oxygen content of mixed venous blood (**C_vO_2**) even if both the F_iO_2 and the shunt fraction are constant. Any condition that **reduces the DO_2 while the $\dot{V}O_2$ remains constant** (e.g. reduced Hb and/or C.O., changes in the P_aO_2/S_aO_2 relationship) *or* **increases the $\dot{V}O_2$** (e.g. fever, shivering, thyrotoxicosis, infusion of drugs with a strong beta-adrenergic effect) without a corresponding increase in DO_2 cause a further **fall in the O_2 content** of arterial blood even if the degree of pulmonary dysfunction stays constant.

On the other hand, if **S_vO_2 increases** (e.g. if C.O. increases while O_2 consumption is kept constant, *or* O_2 consumption decreases while C.O. is stable), the C_aO_2 will rise. Thus, if the C_aO_2 becomes critically low in patients with severe respiratory failure, **manipulating the $DO_2/\dot{V}O_2$ ratio** (e.g. administration of inotropes, cooling, see above) may have beneficial effects on arterial oxygenation.

THE COMBINED EFFECT OF SHUNT AND V/Q DISTURBANCES ON BLOOD OXYGENATION IN THE LUNGS

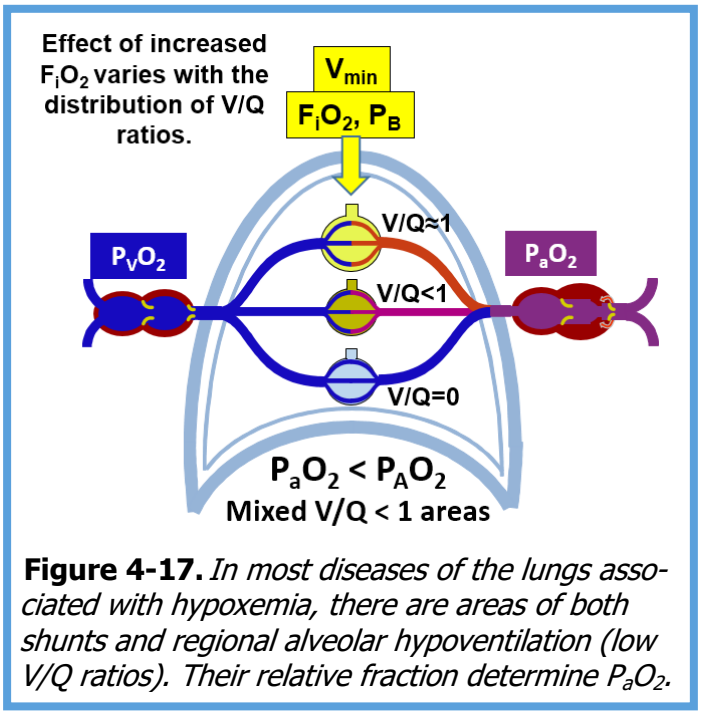

Figure 4-17. *In most diseases of the lungs associated with hypoxemia, there are areas of both shunts and regional alveolar hypoventilation (low V/Q ratios). Their relative fraction determine P_aO_2.*

Most diseased lungs exhibit a heterogeneous mixture of areas with shunt and low V/Q (fig. 4-17). In clinical medicine, the effect of increasing the O_2 concentration in the inspired gas on the P_aO_2 is of greater interest than the calculated magnitude of the shunt *per se*. The effect of increasing the F_iO_2 reflects the severity of the pulmonary dysfunction, provided no extra-pulmonary shunts exists (see above). The degree of lung dysfunction also has a prognostic value, the *precision* of using lung dysfunction as the *only* prognostic parameter is, however, unsatisfactory and the quest for better prognostic tools goes on (109).

Three methods for quantifying failure of pulmonary gas exchange.

When treatment effects on patients with respiratory failure are investigated, the scientific precision of comparisons between treatment and control groups is increased when patients can be stratified according to the severity of disease. Estimations of the magnitude of the pulmonary dysfunction (i.e. the combined effect of pulmonary shunt and low V/Q areas) are therefore important in such research. Common to all the three methods below is the need for knowing the F_iO_2 with a reasonable degree of accuracy (see also Part 4-4). None of them are precision tools

but represent a *rough estimate* of the severity of the pathological process in the lungs and thus the degree of gas exchange failure.

The ratio between P_aO_2 and F_iO_2.

This is the simplest and most commonly used method for patients with acute respiratory failure. It estimates the effect of increasing the F_iO_2 on the P_aO_2 by calculating the ratio between P_aO_2 and F_iO_2 (the P_aO_2/F_iO_2 ratio); a higher F_iO_2 needed to obtain a given P_aO_2 indicates a larger fraction of true shunt. In a person with P_aO_2 = 10 kPa (75 mmHg) and breathing gas with a F_iO_2 = 0.5 (50% O_2 in inspired air), P_aO_2/F_iO_2 will be 10/0.5 = 20 kPa *or* 75/0.5 = 150 mmHg. This method assumes relatively normal CO_2 levels and barometric pressure, and ignores the contribution of changes in C.O. and $\dot{V}O_2$ to the P_aO_2 (see above). The accuracy is reduced in patients with hypercarbia or significant deviations of the $DO_2/\dot{V}O_2$ ratio. On the other hand, in settings where both the CO_2 and Hb usually are controlled (as in a ICU), it is a simple and robust method. The magnitude of the calculated ratio depends on the units employed for gas pressure measurements (kPa or mmHg).

The alveolar-arterial PO_2 difference.

This method, calculating the (P_AO_2-P_aO_2), requires that P_AO_2 can be calculated with a reasonable accuracy; the effect of CO_2 and barometric pressure on the P_AO_2 have then been taken into consideration, making this method **more precise**. The effect made by variations in C.O. and $\dot{V}O_2$ on the O_2 content of mixed venous blood (see above) is, however, still not included. Also for this type of calculation, the magnitude of the difference depends on the unit used for gas pressure. For bedside purposes and at atmospheric pressures close to sea level, the simplified version of the alveolar air equation (see above) may be utilized; it is, however, best suited for use in countries where blood gas tensions are given in kPa.

The "classical" shunt fraction calculation.

This equation (Berggren's equation, ref. 110) is the most accurate alternative *when the predominant V/Q abnormality is shunting*. It assumes, however, a "black-or-white – shunt *vs* normal gas exchange" situation, analogous to that of cardiovascular shunts (see above). Accordingly, a large percentage of areas with medium to low V/Q ratios in the lungs reduces the accuracy of this method; it is, therefore, best suited for patients with acute respiratory failure where shunts often are the predominant cause of hypoxemia. The calculation requires not only that P_AO_2 has been computed, but also accurate measurement of PO_2 and SO_2 in both arterial and mixed venous blood (see above). Mixed venous blood can only be obtained by catheterization of the right ventricle or pulmonary artery; substituting such samples with blood from a central vein introduces errors whose magnitude is difficult to predict (111), see also Part 3-4 and Part 5-4.

Calculation of the shunt fraction.

The blood passing through regions with pulmonary shunt (similar to **SF** in fig 4-14B) maintains its mixed venous oxygen content. Blood that passes through capillaries supplying alveolar areas with a normal function leaves these regions with an oxygen content ($\mathbf{C_cO_2}$) determined by the oxygen pressure in the alveolar gas, assuming P_cO_2=P_AO_2. The S_cO_2 is calculated from the P_AO_2, utilizing the HbO_2 dissociation curve, with necessary corrections for arterial pH and CO_2. This corresponds to the transpulmonary blood flow (**TB**) in fig 4-14. The relative magnitude of the two fractions of the total flow determines the final oxygen content of arterial blood (C_aO_2).

If the flow through the shunt fraction equals **Qs** in and the total flow through the lungs equals **Qt (SF +TB** in fig 4-14B), the **shunt fraction is Qs/Qt**. The flow of normally oxygenated blood = Qt — Qs, and we can construct the following equation:

$(\mathbf{Qs} \times \mathbf{C_vO_2}) + (\mathbf{Qt} - \mathbf{Qs}) \times \mathbf{C_cO_2} = \mathbf{Qt} \times \mathbf{C_aO_2}$

If we multiply out the equation and re-arrange the factors, we get:

$Qt \times (C_cO_2 - C_aO_2) = Qs \times (C_cO_2 - C_vO_2)$.

After dividing by Qt and $(C_cO_2 - C_vO_2)$, we get the shunt fraction

$$\frac{\mathbf{Q_s}}{\mathbf{Q_t}} = \frac{\mathbf{C_cO_2 - C_aO_2}}{\mathbf{C_cO_2 - C_vO_2}}$$

CONDITIONS ASSOCIATED WITH HYPERCARBIA

Hypercarbia with normal alveolar-capillary units.

Hypoventilation (i.e. reduced alveolar minute ventilation) is the most common cause of hypercarbia in persons with essentially normal lung function and a CO_2 production in the normal range (see also fig. 4-13). Hypoventilation also reduces the supply of fresh O_2 to the alveolar gas; the increase in PCO_2 is therefore accompanied by a proportional reduction in PO_2, as described by the alveolar gas equation.

Increased CO_2 load may be due to increased production secondary to *increased metabolic rate* (e.g. physical exertion, high fever, thyrotoxicosis, increased generation of CO_2 from bicarbonate during acidosis), or insufflation of CO_2 gas during endoscopic procedures. None of the above cause hypercarbia in persons with a normal ventilation response; they may, however, do so in persons with a reduced ability to increase ventilation (e.g. chronic lung diseases, drug effects, neuromuscular diseases).

Hypercarbia due to dysfunctional alveolar-capillary units.

Increased alveolar dead space, i.e. regions where alveolar ventilation volumes are normal or increased but have no perfusion (alveolar dead space fraction = **ADF** in fig. 4-18B). Such areas are functionally analogous to the anatomical dead space, i.e. there is a gas flow, but no exchange of gas between the gas phase and the blood. In such non-perfused areas, the V/Q ratio is defined as infinity (= ∞). In a theoretical "pure" situation, assuming that all perfused alveoli receive normal ventilation volumes and all the blood flowing through the lungs passes by ventilated alveoli, the blood exiting the lungs will have a PO_2 close to that in the alveoli ((A) in fig. 4-18B, fig. 4-16C). A normal P_ACO_2 requires, however, increased ventilation volumes; if the P_ACO_2 increases, the alveolar, and thus the arterial, PO_2 decreases (see below).

If a substantial increase in alveolar dead space occurs, the organism has two options for excreting the same amount of CO_2 as before, i.e. the same amount as that generated by the tissues.

- **Increasing the total lung ventilation** to a level where ventilation of the well perfused alveoli can keep the P_ACO_2 normal and thus maintain a normal P_aCO_2, *or*
- **Allow the P_ACO_2 (and thus the P_aCO_2) to increase**. A higher CO_2 concentration in the alveolar gas increase the CO_2 concentration in the expired air, a smaller ventilation volume can then excrete the same amount of CO_2 (see also Part 5, fig. 5-8). These options are shown in fig. 4-19. In fig. 4-18B, 1/3 of the alveolar ventilation volume does not participate in CO_2 excretion, and the remaining 2/3 of the alveoli must excrete the whole metabolic load of CO_2.

Localized alveolar areas with substantially reduced perfusion – high V/Q ratios (see fig. 4-18C).

In such alveoli, some CO_2 is excreted, but the amount is much lower than normal and the CO_2 concentration in the gas exiting from such alveoli during expiration is low. As for alveolar dead space, the PO_2 in the blood leaving the perfused alveoli is similar to the P_AO_2 ((**D**) in fig. 4-18C). The options available to the organism for dealing with this condition are similar to those for alveolar dead space.

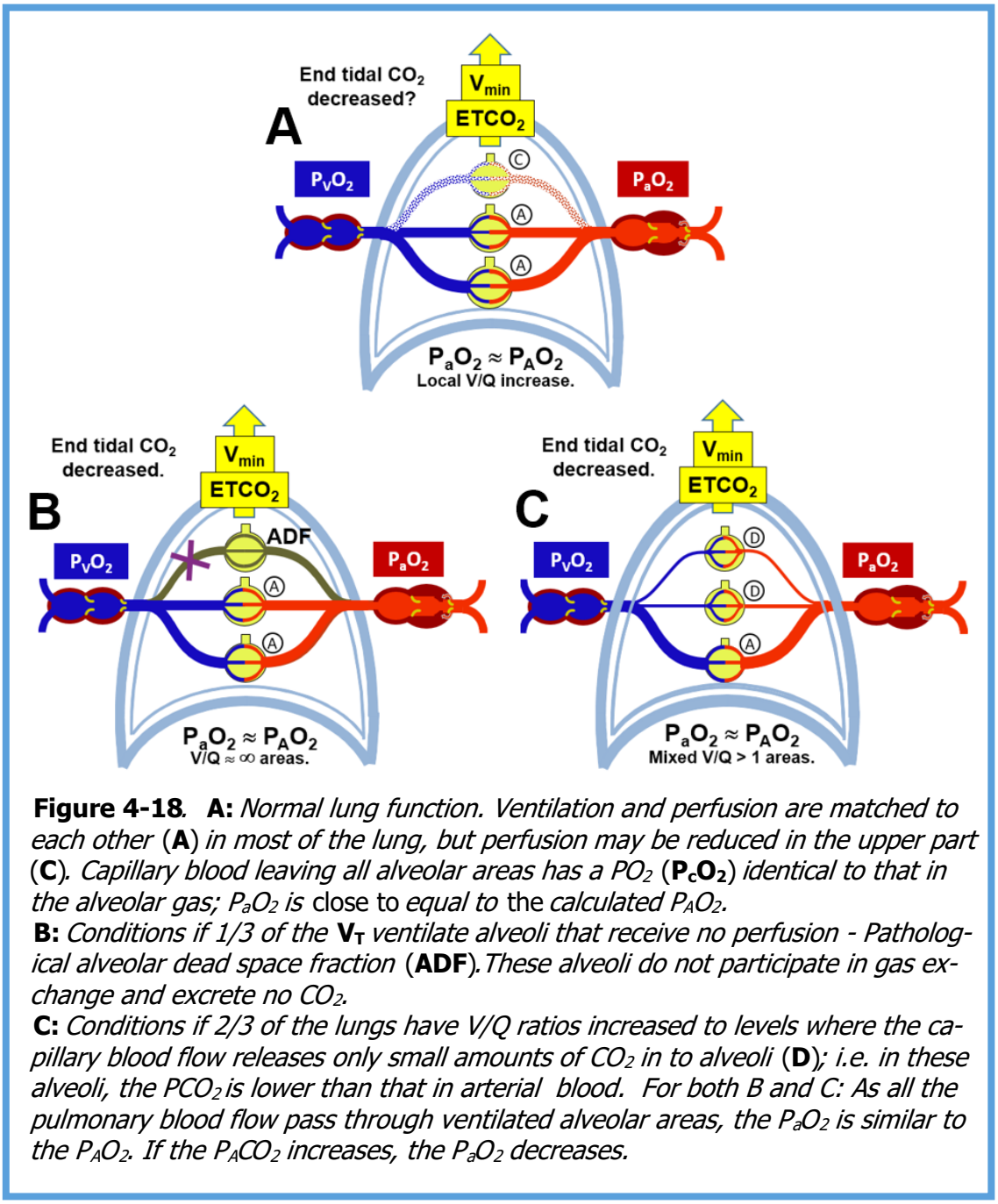

Figure 4-18. **A:** *Normal lung function. Ventilation and perfusion are matched to each other* (**A**) *in most of the lung, but perfusion may be reduced in the upper part* (**C**). *Capillary blood leaving all alveolar areas has a* PO_2 (**P_cO_2**) *identical to that in the alveolar gas;* P_aO_2 *is* close to *equal to* the *calculated* P_AO_2.
B: *Conditions if 1/3 of the* **V_T** *ventilate alveoli that receive no perfusion - Pathological alveolar dead space fraction* (**ADF**). *These alveoli do not participate in gas exchange and excrete no* CO_2.
C: *Conditions if 2/3 of the lungs have V/Q ratios increased to levels where the capillary blood flow releases only small amounts of* CO_2 *in to alveoli* (**D**); *i.e. in these alveoli, the* PCO_2 *is lower than that in arterial blood. For both B and C: As all the pulmonary blood flow pass through ventilated alveolar areas, the* P_aO_2 *is similar to the* P_AO_2. *If the* P_ACO_2 *increases, the* P_aO_2 *decreases.*

Physiological alveolar dead space and high V/Q ratios.

With normal resting blood flow through the lungs, the apical parts of normal lungs are hypo- or non-perfused when sitting or standing (West's model, fig. 4-10). The V/Q ratio in such alveolar areas normally varies between V/Q = ∞ and V/Q = 1.5 or higher; in opposition to pathological

dead space, such areas may disappear within seconds if the pulmonary blood pressure increase and secure a normal blood flow also in the uppermost lung regions.

Pathological alveolar dead space and high V/Q ratios.

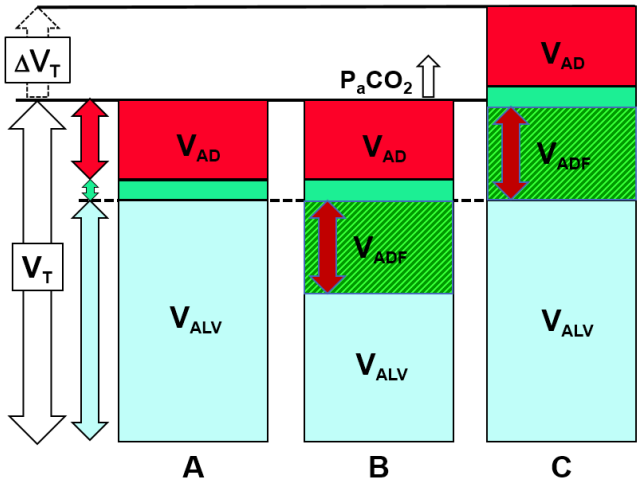

Figure 4-19. A: *Normal distribution of the tidal volume to anatomical dead space* (**V_{AD}** - *red*), *alveolar gas volume* (**V_{ALV}** - *light blue*) *and physiological alveolar dead space* (**V_{ALVD}** - *green*). **B:** *If the alveolar dead space* (**V_{ADF}**) *increases and the V_T stays unchanged, the gas volume ventilating perfused alveoli decreases and the PCO_2 increases.* **C:** *Increasing the tidal volume* (**ΔV_T**) *increase ventilation of perfused alveoli and may attenuate or abolish the increase in P_aCO_2.*

Alveolar dead space caused by disease occurs as a result of temporary or permanent changes in pulmonary vessels passing by ventilated alveoli. Such pathological impediment to perfusion does *not* disappear with increased pulmonary blood flow. It may be due to areas with permanent loss of perfusion due to tissue destruction or permanent vessel obstruction (V/Q = ∞) or to areas with partial vascular obstruction (e.g. micro thrombosis, partial embolization). The effect of the latter may disappear if re-perfusion of obstructed areas is achieved. All types of perfusion disturbances can be expected in diseased lungs (fig. 4-20).

Dead space and very high V/Q ratios are common in patients with chronic obstructive lung disease (COPD), and many of those cannot compensate by increasing ventilation (see below). In acute disease (e.g. pulmonary embolization, pulmonary microthrombosis), most individuals with previously normal lung function can compensate by increasing the ventilation and do not develop hypercarbia in the initial phase. If respiratory muscle fatigue develops, however, hypercarbia may occur.

Consequences of very high V/Q ratios for CO_2 excretion.

If about 1/3 of the alveoli are non-perfused (V/Q = ∞) and about 1/3 are hypoperfused with a flow that permits about 50% of normal excretion of CO_2 (low V/Q), the last 1/3 of the alveolar areas receive a blood flow (and thus also an amount of CO_2) that is about 2.5 times normal (fig. 4-18). As fewer alveoli (depicted as 2/3 of normal in fig. 4-18) are available for excretion of CO_2, these must increase their ventilation for the blood to excrete the same volume of CO_2 as before during the passage through the lungs. If this does not occur, the mean PCO_2 in such alveoli increases. The P_AO_2 also decreases, causing a P_aO_2 decrease in the perfusing capillaries proportional to the increase in P_ACO_2. As for V/Q dysfunction causing hypoxemia, a wide variety of V/Q ratios may be found in both normal and diseased lungs (fig. 4-20).

Quantification of the dead space – calculation examples.

The methods available measure the total gas volume of the airways where very little or no gas exchange occurs, that is, *a combination of the anatomical and alveolar dead space.* The expired air coming from these areas is largely identical to the inspired air from the previous inspiration

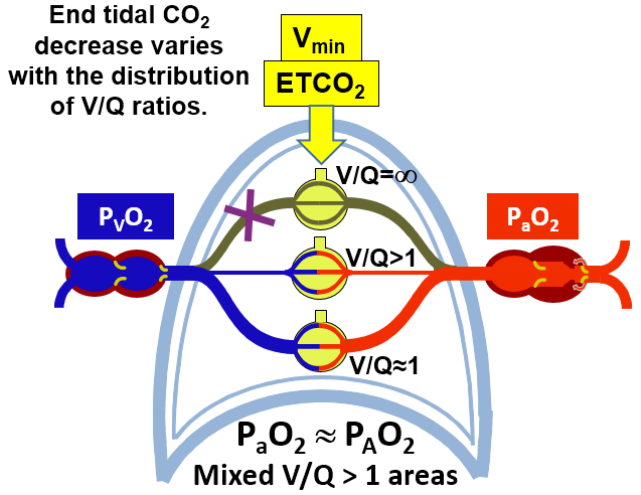

Figure 4-20. *In most diseased lungs associated with reduced end-tidal CO_2, there are areas of both dead space and regional very high V/Q ratios. If P_ACO_2 stays normal, P_aO_2 remains in the normal range.*

(in a three-compartment model, 1/3 rebreathed alveolar air and 2/3 ambient gas, see fig 4-8), and dilutes the CO_2 in the gas expired from alveoli in which normal gas exchange takes place. The larger the dead space, the more dilution of CO_2 in both the mixed expired air and the lower the end-tidal CO_2.

Two classical methods for quantifying the dead space volume have been employed. The initial one, analyzing the CO_2 content of the expired air (112) has later replaced by analyzing the CO_2 content of expired air *and* blood (113). The other one analyses the nitrogen content of the expired air after inhalation of 100% O_2 (114). The most common method today is that of Enghoff (113), where the P_aCO_2 is assumed to represent the mean value of P_ACO_2 in alveoli that are both ventilated *and* perfused. To perform the calculations, the PCO_2 in the whole expired tidal volume (P_ECO_2) and the arterial blood must be known.

If the dead space is expressed as the fraction of the tidal volume (V_T) that ventilates dead space alveolar areas (V_D), the equation becomes

$V_D/V_T = (P_aCO_2 - P_ECO_2)/P_aCO_2$.

If there is no alveolar dead space, the tidal volume is 500 ml and the anatomical dead space is 150 ml, the calculated **V_D/V_T** will be

150/500 = 3/10 *or* **30%** *or*, inserting PCO_2 values in kPa: (5.3-3.7)/5.3**= 0.3**

Given a total dead space of 250 ml (anatomical 150 ml and alveolar 100 ml), the same tidal volume and a P_aCO_2 of 6 kPa, and a P_ECO_2 of 3 kPa, the equation becomes

V_D/V_T= (6 – 3)/6 **= ½ or 50%.**

As for the shunt equation above, this calculation assumes that there are only two types of ventilated airspace: Those with normal and those with no perfusion. In reality, the dead space effect is caused by a heterogeneous mixture of ventilated alveoli with different perfusion flows, where the V/Q ratio ranges from 1.5-2 up to infinity, and true V/Q = ∞ areas (fig 4-20).

Simple qualitative estimates, based on end-expiratory CO_2 (as measured by capnography, minute ventilation, and arterial CO_2, may also be performed. Under normal circumstances, the CO_2 in end-expiratory gas is numerically similar (in % *or* kPa) to P_aCO_2.

- *The lower the PCO_2 in end expired air, relative to the arterial blood level, the greater the alveolar dead space effect.*
- *The higher the minute ventilation necessary to keep PCO_2 in the normal range, the greater the dead space effect.*

End-expiratory CO_2 may deviate substantially from arterial PCO_2 in patients with pulmonary diseases that result in significant increases in dead space, and also in certain patient groups with healthy lungs (e.g. hypotensive patients with low pulmonary vascular resistance and increased

airway pressure). The latter type of effect will be particularly noticeable in the sitting/semi-recumbent position (e.g. some neurosurgical patients under hypotensive anesthesia).

In certain patients (e.g. those with severe cerebral edema), accurate and continuous monitoring of the blood CO_2 level is particularly important. If end-tidal CO_2 is used as a surrogate for P_aCO_2, the relationship between end-tidal and arterial CO_2 must be established *before* accepting that ventilation should be controlled in accordance with the CO_2 values read from a capnograph. Also, the relationship between these two parameters must be re-examined every few hours, with more frequent comparisons if the clinical condition changes.

Impact of dead space and low V/Q ratios on CO_2 and O_2 in arterial blood.

The final effect of alveolar dead space on CO_2 and O_2 depends on whether the minute ventilation of the perfused alveoli increases to an extent where it compensates for the lack of CO_2 excretion in non-perfused alveoli (fig. 4-15C). If P_aCO_2 rises beyond 11-12 kPa within a few minutes or hours, patients with such blood levels often grow lethargic or even become unconscious (often referred to as carbon dioxide narcosis or CO_2 narcosis). This may be misinterpreted as an improvement of lung function as the ventilation appears less labored. The PCO_2 may, however, be rising rapidly and cause respiratory acidosis (possibly with a normal S_pO_2 if supplemental O_2 is

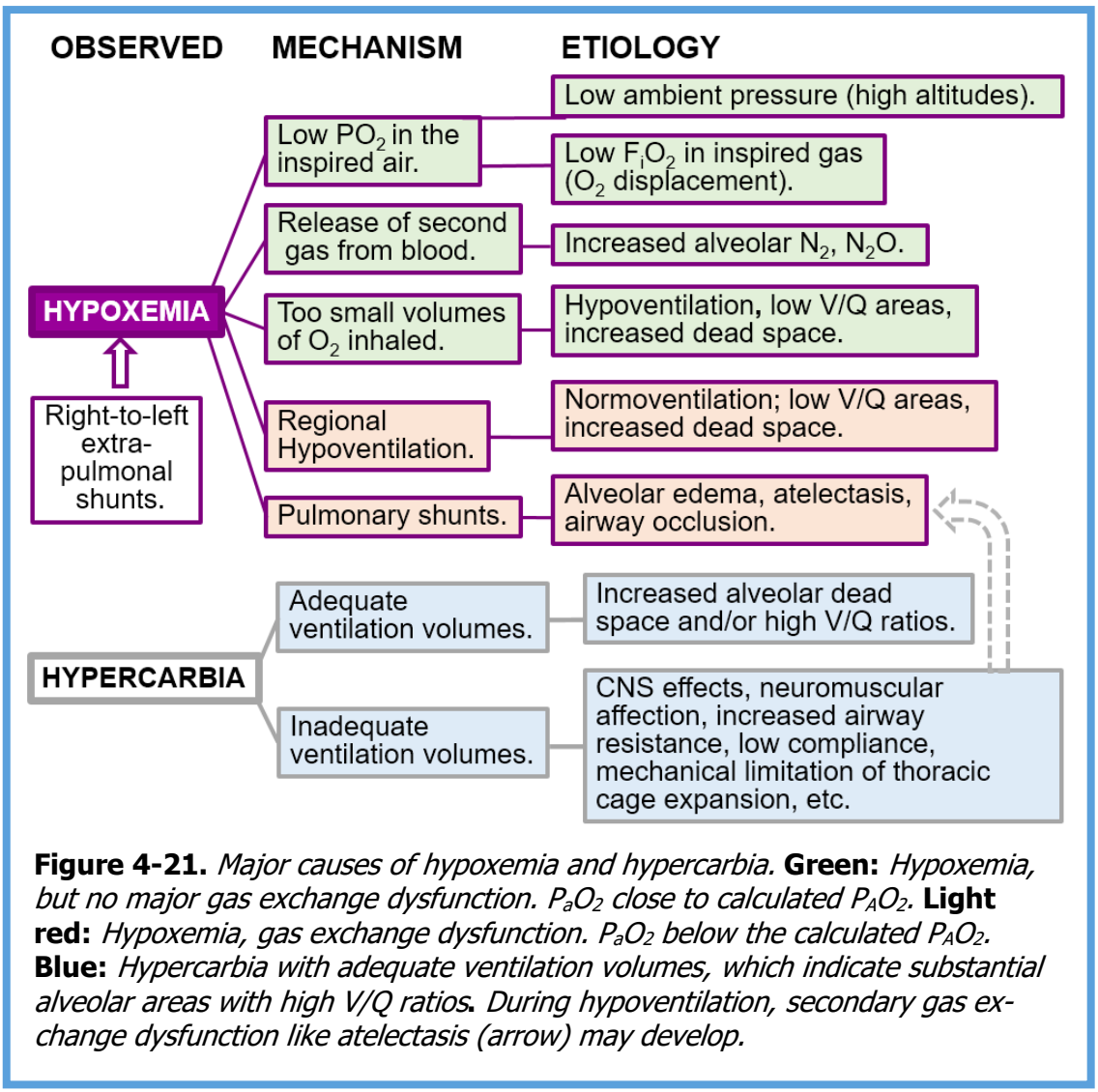

Figure 4-21. *Major causes of hypoxemia and hypercarbia.* **Green:** *Hypoxemia, but no major gas exchange dysfunction. P_aO_2 close to calculated P_AO_2.* **Light red:** *Hypoxemia, gas exchange dysfunction. P_aO_2 below the calculated P_AO_2.* **Blue:** *Hypercarbia with adequate ventilation volumes, which indicate substantial alveolar areas with high V/Q ratios. During hypoventilation, secondary gas exchange dysfunction like atelectasis (arrow) may develop.*

given, see calculations above). The clinical effect of high P_aCO_2 levels varies between individuals and with the time factor. Some patients may be wide awake and in apparently good clinical condition with $PaCO_2$ levels up to 17-20 kPa (128-150 mmHg), provided they are receiving supplemental O_2 and that the increase in CO_2 has progressed slowly.

V/Q mismatch in disease.

A simplified overview of the various causes of hypoxemia and hypercarbia is shown in fig. 4-21. In most types of respiratory failure, the V/Q ratios are highly heterogeneous, with some areas pri-marily consisting of shunt and low V/Q conditions ($0 < V/Q < 1$), and others of dead space and high V/Q conditions ($1 < V/Q < \infty$).

Exceptions are conditions where localized airway occlusion, atelectasis, or alveolar flooding are the sole cause of alveolar-capillary dysfunction. The initial type of pathological dysfunction may induce other types of change; e.g. the weight of fluid-filled lung tissue (alveolar and interstitial edema) may compress more dependent areas and create atelectasis. Also, interstitial edema may increase the local airway resistance, and airway occlusion creates atelectasis. If a substantial number of pulmonary vessels are occluded (e.g. major pulmonary emboli), the hydrostatic pres-sure in the remaining perfused vessels may become high enough to create interstitial and alveolar edema, which then reduces the P_aO_2 further; the increased PAP may induce failure of the right ventricle as well.

If both perfusion and ventilation of the same alveolar areas cease (e.g. surgical removal of lobes or lungs), and both are re-directed to normally functioning parts of the lungs, there are no areas of V/Q mismatch. The arterial PO_2 and PCO_2 levels may not change unless the hydro-static pressure in the remaining pulmonary tissue becomes high enough to create interstitial or alveolar edema (see also Part 4-3). The total alveolar-capillary surface is, however, re-duced. The capacity for increasing ventilation volumes is limited, and the reduced pulmonary vascular bed cannot accommodate significant increases in C.O. without a major increase in PA pressures and increased RV workload (see also below).

4-3. RESPIRATORY FAILURE (RF) AND ITS CONSEQUENCES

INTRODUCTION.

Pulmonary dysfunction spans from a slight reduction in blood oxygenation and/or CO_2 excretion of little importance during everyday activities, to a total failure of blood oxygenation leading to life-threatening hypoxemia within a few minutes. It comprises a wide variety of conditions and diseases, caused by either *dysfunction* (or non-function) of the *pulmonary ventilation in general*, major *maldistribution of ventilation vs perfusion* (i.e. the *V/Q ratios) in the* alveolar-capillary units, *or both*. If dysfunction reaches a level where arterial hypoxemia and/or hypercarbia threaten the normal function of the organism, the patient is in **Respiratory failure (RF).** Such failure may be classified according to ***i)*** the pathophysiological mechanisms involved, ***ii)*** the effect on arterial blood gases, and ***iii)*** the timelines involved in development of failure.

Hypoxemia in disease.

Hypoxemia may occur in persons with perfectly normal lungs if the inspired gas has a reduced O_2 content (Part 4-2). When caused by **disease,** hypoxemia is caused by

- **Hypoventilation,** where the alveolar-capillary function in the initial phase (i.e. before the potential formation of atelectasis) may be normal.
- **Passage of a fraction** of the pulmonary blood flow through areas with **localized alveolar hypoventilation.**
- **Passage of a fraction** of the pulmonary blood through areas with **intrapulmonary shunting.**

For details of the pathophysiology, see Part 4-2.

Hypercarbia in disease.

- **Hypoventilation** (see above). Hypercarbia occurs when the ventilation volumes are too low to be able to excrete the amount of CO_2 generated by the tissue metabolism without increasing the CO_2 content in the expired gas, and thus in the alveoli and arterial blood.
- **Localized hypo- or non-perfusion**, where CO_2 must be excreted by a reduced number of alveoli, and the ventilation apparatus fails to increase the ventilation enough to compensate for this.

The clinical presentation of respiratory failure.

Hypoxemia is the cardinal symptom of respiratory failure and may be visible as skin and/or mucous membrane cyanosis in patients with an Hb > 5-6 g/dl. **Hypercarbia** does not cause specific symptoms (see below) but may be suspected when hypoventilation is observed in normothermic patients.

The **clinical symptoms of acute respiratory failure (ARF)** and acute **exacerbation of chronic respiratory failure (CRF)** vary in both etiology, severity, and time frame for its development. **Typical symptoms** associated with ARF in awake patients are

- **Rapid, labored breathing** (> 35 bpm) with the use of accessory respiratory muscles (breathlessness), speaking in complete sentences during one exhalation is difficult.
- **Tachycardia.**
- **Anxiety, restlessness, and sweating.**
- **Confusion and sometimes loss of consciousness** may be a result of severe hypoxemia, but cerebral symptoms may also be due to high PCO_2 levels in the blood (CO_2 narcosis, see above). During hypercarbia, hypoxemia may be absent if supplementary O_2 is administered.

If **airway obstruction** is part of the etiology

- **Wheezing** may be prominent. A sudden stop of wheezing may signal improvement, but may also be a danger signal, indicating *either* a severe reduction in ventilatory effort *or* the conversion of *obstruction* into airway *occlusion*.

If *severe* **airway obstruction or occlusion** is part of the problem

- **Paradoxical respiration**, i.e. the front of the thoracic cage is sucked in while the abdomen expands as a result of contraction of the diaphragm during forced inspiration, often accompanies obstruction and occlusion of the airways.

The respiratory and circulatory repose to acute hypoxemia and hypercarbia is reduced by about 50% and 40%, respectively, in older persons (65 and 73 years) compared to younger persons (23 to 30 years)(115). In *sedated* or *comatose patients*, some or all of the above symptoms may be lacking.

Some of the clinical symptoms of respiratory distress with severe hypoxemia are non-specific symptoms of cerebral hypoxia and are shared with other conditions; hyperventilation and cerebral symptoms may also occur in various shock states. Labored breathing and hyperventilation in response to severe *metabolic acidosis*, after *cerebral insults* leading to local cerebral acidosis, and during *psychogenic hyperventilation*, can be misinterpreted as respiratory failure. During hyperventilation due to acidosis, however, deep breathing (large tidal volumes) with normal respiratory frequency is more common than tachypnea. Cyanosis, especially when the hypoxemia is verified by blood gas analysis and/or S_pO_2 measurements, usually confirms the diagnosis of respiratory failure.

The etiology of respiratory failure is sometimes obvious, as in acute alveolar edema in a person with known severe LV failure or severe stridor in a patient with known asthma. In patients with hypoxemia and signs of infection and/or generalized inflammation, acute pulmonary failure classified as Acute Respiratory Distress Syndrome (ARDS – see below) is a likely diagnosis. In the latter case, the underlying process needs to be clarified rapidly, as the most successful treatment of this syndrome is early recognition and treatment of the underlying cause *before* the inflammatory processes that lead to pulmonary dysfunction becomes too severe.

WAYS TO CLASSIFY RESPIRATORY FAILURE (RF)

By focusing on the two fundamentally different pathophysiological changes causing hypoxemia and/or hypercarbia

- **Hypoventilation,** where the composition of the alveolar gas *in all parts* of the lung changes as a result of *reduced* tidal- and minute *ventilation volumes*. During the initial phase, the **alveolar-capillary unit** structure and function may be intact.
- **Failure of the gas exchange properties of the alveolar-capillary units** (i.e. increased alveolar areas with very small or no ventilation, or with very small or no perfusion – increased V/Q *heterogeneity*); the *ventilation volumes* are often *normal or increased* in the initial phase.

The above conditions may occur simultaneously *or* independently from each other. In clinical medicine, a mixture of ventilation failure *and* deranged gas exchange may be present in patients who require urgent medical attention.

Failure of the alveolar-capillary units may be

- **Temporary,** and with essentially **preserved structure of the alveolar-capillary units** (e.g. hydrostatic pulmonary edema, bronchospasm, positive pressure pneumothorax, partial airway occlusion). In survivors**,** it is usually reversible within minutes to hours if the underlying process can be remedied rapidly.
- **Temporary,** but with **acute inflammatory damage to the alveolar-capillary units** (acute inflammatory processes due to intrapulmonary or extra-pulmonary disease processes, e.g. acute respiratory distress syndrome, ARDS below). The gas exchange function usually remains compromised for days or weeks, in survivors, most of the damage ultimately heals and the patients regain adequate, but not always normal, lung function.
- **Irreversible, with major structural damage,** as a result of *either* acute tissue damage (e.g., inhalation of corrosive gases, major lacerations due to trauma, uncontrolled fibrotic processes) or *chronic inflammatory processes.* The acute phase of such respiratory failure continues as a chronic phase in survivors.

By focusing on the timelines: acute and chronic respiratory failure.

- **Acute RF (ARF)** may develop within *seconds to minutes* (e.g. total airway occlusion, massive pulmonary embolization), within *minutes to hours* (e.g. pulmonary edema due to acute left ventricular failure), or *hours to days* (e.g. inflammatory conditions underlying the development of the acute respiratory distress syndrome (ARDS)). Conditions leading to ARF often have a large element of intrapulmonary shunts, and can often be classified as a t*ype 1 respiratory failure* (see below for definition) during the initial phase of the disease.
- **Chronic RF (CRF)** may occur in the aftermath of acute irreversible lung injury, but is most often a result of chronic inflammatory processes in the airways or pulmonary tissue. The condition normally develops over months to years (e.g. chronic obstructive pulmonary disease (COPD), cystic fibrosis, pulmonary fibrosis, asthmatic changes, see below), but patients may have acute exacerbations with similar timeframes as for ARF above. The major pathophysiological change in chronic RF is an increase in alveolar areas where extreme V/Q ratios, both low and high, are more numerous and heterogeneously distributed than in normal lungs. Acute exacerbations of chronic disease (acute-on-chronic RF) often results in an increased fraction of intrapulmonary shunt.

By focusing on the effect on arterial blood gases (P_aO_2, P_aCO_2).

Patients with respiratory failure have traditionally been classified according to *consequences for the* **PO_2** *and* **PCO_2** *in the arterial blood* (hypoxemia, hypercarbia).

RF type 1 and type 2.

To ensure a common understanding of when respiratory dysfunction should be defined as failure, limits of P_aO_2 decrease and P_aCO_2 increase have been proposed, and respiratory failure has traditionally been classified into two main categories (see below). The P_aO_2 and P_aCO_2 levels employed for diagnosis of failure diverge somewhat, however, between various authors, guidelines, and handbooks; the borderline P_aO_2 may be given as a value between 6.7 and 8 kPa (50-60 mmHg), that of P_aCO_2 between 6 and 6.5 kPa (45-50 mmHg).

A commonly used definition of respiratory failures (116, 117) is

- **Respiratory failure (RF) type 1**, where the main problem is **hypoxemia**, is usually defined as **P_aO_2 <8 kPa** (60 mmHg) when breathing **ambient air at sea level**, i.e. a

P_aO_2/F_iO_2 ratio of 8/0.209 ≈ 38 kPa (287 mmHg) *or* a P_AO_2-P_aO_2 difference of 5.3 kPa (40 mmHg). The ability to maintain or increase ventilation in response to hypoxemia is preserved; **P_aCO_2 is therefore normal or subnormal.**

- **Respiratory failure (RF) type 2**, where *both* oxygenation and CO_2 excretion are affected. The definition of **hypoxemia** is **similar to RF type 1** above; in addition, the capacity for the excretion of CO_2 is reduced. The **P_aCO_2 increase is defined as > 6.5 kPa (50 mmHg)** *despite* the increased respiratory drive created by hypoxemia. The **ventilation volumes** may be *reduced*, *normal* or *increased*.

This type of classification defines the*here-and-now state* of pulmonary failure as quantified by a blood gas analysis, and does not represent an etiological grouping. Most patients in the RF type 1 group will, however, have acute respiratory failure, while those in RF type 2 tend to have chronic failure. Patients with severe asthma attacks (see below) or acute reductions in lung compliance may fulfill the criteria for RF type 1 in the initial phase, and then the RF type 2 criteria later on, when initial hypoxia-driven hyperventilation wanes as respiratory muscle fatigue develops. In patients with **Acute Respiratory Distress Syndrome (ARDS)**, the stratification of disease severity is based on three levels of P_aO_2 relative to the F_iO_2, the P_aO_2/F_iO_2 ratio (see above and ARDS below for details).

Interpretation of blood gas analysis

Accurate analysis of PO_2 and PCO_2 (blood gases) are rapidly available on-site in most emergency rooms and ICUs of larger hospitals in industrialized countries. Measurements of S_aO_2 by pulse oximetry (S_pO_2) is widely available also in pre-hospital settings, but may not be reliable in circulatory unstable patients. Measurement of end-tidal CO_2 may also be available, but is accurate only in patients with tight-fitting masks, endotracheal tubes or tracheostomy cannulas. Whether the measured values are representative of the P_aCO_2 must be verified by analysis of arterial blood.

Knowing the F_iO_2 with a reasonable accuracy is necessary for estimating the alveolar-arterial difference, a steady-state condition is necessary for reliable calculations. As a rule of thumb, P_aO_2 will stabilize within 10 minutes after a change in F_iO_2 and/or ventilation modus in most patients, while P_aCO_2 can be expected to stabilize within 30 minutes. In patients with unstable circulation or advanced COPD, these periods may be longer. When evaluating the results of blood gas analysis, i.e. when using the levels of P_aO_2, P_aCO_2, and pH as an estimate of the severity of the respiratory failure, the values must be judged in light of the *clinical picture*, estimated or measured *ventilation volumes* and the actual *F_iO_2* at the time of sampling.

Simple rules of thumb for initial evaluation are

- A **subnormal P_aO_2** in a patient receiving supplemental O_2 at sea level *and* with a normal/subnormal P_aCO_2 is *always* a sign of alveolar-capillary unit dysfunction (i.e. increased V/Q heterogeneity and/or shunt). An age-related P_aO_2 reduction (118) is an expected finding, and does not necessarily imply acute disease; nevertheless, it signals a reduced reserve capacity for pulmonary gas exchange.
- The **effect of increasing the F_iO_2 on the P_aO_2** (or S_pO_2) gives a semi-quantitative estimate of the relative magnitude of alveolar areas with shunts (modest effect, normalization not possible with shunt fraction > 0.3) and low V/Q (larger effect, normalization often possible).
- While the **P_aO_2** value is important as an indicator of the state of pulmonary gas exchange, it does not, *per se* , disclose much information about the O_2 delivery capacity (which mostly depends on the **S_aO_2**, **Hb**, and **C.O.**, see Part 2-3) relative to the needs of the organism.

- The **P_aCO_2 values** must be judged relative to the ventilation volumes (measured or estimated clinically) if assumptions about pathological increases of areas with high V/Q alveoli and/or alveolar dead space are to be made.
- **Increased P_aCO_2** (which is close to the mean P_ACO_2 in perfused alveoli) is associated with reduced P_AO_2 (see the alveolar air equation), a reduced P_aO_2 when breathing ambient air may in some patients be solely due to hypoventilation of otherwise healthy lungs (a P_ACO_2 of 10 kPa (75 mmHg) corresponds to a P_AO_2 of 7.3 (55 mmHg).
- The **presence and degree of acidosis** in a patient with increased P_aCO_2 may be an indicator of whether the hypercarbia is acute or chronic (see fig 5-9).

For more *details* about arterial blood gas analysis, as well as interpretation of the analysis of blood samples obtained from *other sources* than arterial, see Part 5-4.

CLINICAL CONDITIONS ASSOCIATED WITH HYPOXEMIA

HYPOXEMIA IN PATIENTS WITH ESSENTIALLY NORMAL AIRWAYS AND ALVEOLAR-CAPILLARY UNIT FUNCTION

Hypoventilation: acute and subacute conditions.

During **hypoventilation** *without* a corresponding decrease in metabolic rate, a decrease in P_aO_2, and a simultaneous increase in P_aCO_2 occur (see Part 4-1). Numerous conditions and diseases may cause hypoventilation (or non-ventilation). The most **common** cause of acute life-threatening hypoxemia due to hypoventilation in most western countries is probably an **overdose of narcotic drugs**, the most **dramatic** (but fortunately rare) cause is **acute obstruction/ oc-clusion of the upper airways**.

Some additional etiologies that medical personnel can expect to be confronted with are

- **Central nervous system dysfunction** (e.g. brain trauma and/or hemorrhage, ischemic CNS damage, effects of drugs or toxins other than narcotics).
- **Damage to the upper thoracic or cervical spinal cord** (e.g. trauma, ischemia due to obstruction of spinal arteries, or compression by hematomas).
- **Dysfunction of the peripheral nervous system** (e.g. damage to nerves supplying the diaphragm, polyneuropathies, poliomyelitis).
- **Neuromuscular dysfunction** (e.g. myasthenia gravis, muscle relaxant drugs, toxins like organophosphates, botulinum toxin).
- **Pain on inspiration** (e.g. surgical or traumatic wounds affecting the thorax or upper abdomen)
- **Damage to the thoracic wall** (e.g. multiple costa fractures, flail chest).
- **External restriction of ventilation** (e.g. circular thoracic burns, mechanical compression of the thoracic cage during accidents).
- **Restrictions of lung expansion by reduction of the intrathoracic free space volume** (e.g. pneumothorax, hemothorax, pleura effusions, fibrosis).

In some of the conditions above, damage to the pulmonary tissue and/or development of atelectasis, in addition to hypoventilation, may cause local dysfunction of the alveolar-capillary units, aggravating the hypoxemia.

Chronic conditions.

Conditions like amyotrophic lateral sclerosis (AML), muscle dystrophies, kyphoscoliosis, and restrictions of lung volumes by fibrosis of pleura or lung tissue (e.g., post pleuritic fibrosis, interstitial lung fibrosis) may be associated with chronic hypoventilation (see Chronic Respiratory Failure below). Various types of genetically determined dysfunctions of ventilation regulation may also result in chronic hypoventilation.

The consequences (i.e. the effects on P_aO_2 and P_aCO_2) vary with both the cause and the degree of hypoventilation. Hypoventilation is, over time, usually accompanied by secret stagnation and formation of atelectasis, and may result in permanent V/Q changes in the lungs. Frequent changes in body position (e.g. turning of supine patients) may, to some extent, reduce atelectasis formation.

Respiratory arrest.

Respiratory arrest is the most dramatic cause of acute hypoxemia in persons with essentially normal lungs. As long as the P_AO_2 is higher than the P_VO_2 there is a rapid and homogenous decrease of alveolar PO_2 in the whole lung; when the mean P_AO_2 is reduced to levels equal to the P_VO_2, the alveoli cannot add more O_2 to the perfusing blood and the whole pulmonary circulation becomes a shunt flow. The period before this happens is substantially longer for apnea during *voluntary* breath-holding than for *involuntary* respiratory arrest, see also Part 4-1). During respiratory arrest, there is no steady state, and calculations of P_AO_2 would at best be inaccurate.

Hypoxemia due to obstruction of the airways

The most commonly encountered type of airway obstruction are the attacks of bronchospasm and mucous membrane edema caused by asthma (see below). Intense, asthma-like bronchospasm can also be provoked by anaphylactic reactions (119); the provoking mechanism may, however, differ from that of asthma (120).

Airway obstruction may also be caused by foreign bodies, infections, abscesses, mucous membrane edema, bronchospasm, laryngospasm, blood clots, and dried secretions located in the upper or lower airways; the condition may be hyperacute, acute, or subacute.

Obstruction located *above* the bifurcation, i.e. where the trachea divides into the right and left mainstem bronchi, affects the airflow to both lungs. If increased efforts of respiratory muscles cannot compensate for the increased airway resistance, the V/Q ratio of the whole alveolar airspace is reduced.

From a *therapeutic viewpoint*, a major question is whether an obstruction can be *bypassed* (by insertion of an endotracheal tube, cricothyroidotomy or tracheostomy) or *removed* (using forceps, bronchoscopes and/or other instruments, Heimlich's maneuver, etc.). Obstructions may therefore be divided into

- **Obstructions located in the upper airways,** i.e. all structures close to or above the level of the vocal cords (pharynx, larynx). If obstructions are caused by foreign objects, these can be *removed* using appropriate instruments or by performing the Heimlich maneuver (121, 122). This maneuver is associated with complications, gastric rupture is the most commonly reported problem (reviewed in ref 123). Non-removable obstructions in the upper airways (e.g. tumors, abscesses, edema of mucous membranes) can be *bypassed* by inserting an endotracheal tube or performing a tracheostomy; cricothyroidotomy may represent an alternative in hyper-acute settings under austere conditions.

- **Obstructions located in the lower airways** may be *removed* or *bypassed* using bronchoscopes or similar instruments if they are *located in the trachea or the proximal part of the major bronchi*. Obstructions affecting smaller airways (i.e. too small for endoscopic instrumentation: small bronchi, bronchioles, and alveolar ducts) cannot be remedied by mechanical means, mucous plugs and blood clots can, to some extent, be mobilized and subsequently removed by a combination of postural drainage and percussion (124, 125).
- **Partial obstruction** of airways can be caused by a variety of conditions (126, 127); some may progress to total occlusion. The most common etiologies are compression by mechanical forces, obstruction by foreign objects, hematomas and reactions to infections, inhaled or aspirated corrosives and irritants, or blood-borne pro-inflammatory agents. Some of the more common causes are
  - Tissue edema and space-occupying lesions due to infections in the upper airways (e.g. epiglottitis, supraglottitis, croup, peritonsillar abscesses, hematomas).
  - Aspirated foreign objects lodged in the upper airways.
  - Inhalation of hot smoke or corrosive gases, ingestion of corrosive chemicals.
  - Angioedema (C1 esterase inhibitor deficiency).
  - Tumors.
  - Traumatic hematoma, crushing injuries of the larynx, vocal cord paralysis.
  - Tracheomalacia, where local incomplete/damaged tracheal rings create a "soft" section.

The latter may be especially challenging to diagnose, as tracheomalacia located in the intrathoracic part of the trachea causes expiratory stridor but an extrathoracic location is associated with inspiratory stridor (128). In addition, partial obstruction of the upper airways during sleep (129), especially among obese persons (130) may lead to episodes of hypoxemia.

Total occlusion of airways above the bifurcature - strangulation.

This condition is rapidly lethal if not remedied within minutes. Re-establishing passage of gas through the airways is a prerequisite for any resuscitative efforts to be successful; extracorporeal oxygenation of the blood (see Part 3-3) could theoretically represent a temporary solution but can rarely be organized within a time window of a few minutes.

Such occlusion may be intentional (strangulation by hands, ropes, etc.); if the arteries supplying the brain are also compressed, the person may become unconscious within seconds (see also Part 3-3) *before* hypoxemia becomes severe. Accidental suffocation may be caused by relaxation of the tongue in sedated or unconscious persons (131), plastic bags over the head (132), aspiration of pieces of food, etc. (133, 134). Laryngospasm is a spasmodic closure of the vocal cords (135) that may cause acute total airway occlusion. It is usually a complication during anesthesia (136) but the reflex may be provoked by irritating stimuli also in other situations.

Chronic and sub-acute obstructions may progress to total occlusion. Epiglottitis can cause subtotal or total obstruction of the upper airways; it is most dangerous in children, because of their narrower airways, but also adults can suffer total airway occlusion. It is usually caused by an infection with Haemophilus Influenza; after vaccination against this agent was introduced, epiglottitis has become a rare disease in industrialized countries (137). Subglottic edema and croup (133) may also cause severe airway obstruction.

Total occlusion of a large airway distal to the bifurcation creates an intrapulmonary shunt within minutes, somewhat similar to the conditions during one-lung ventilation in lung surgery (138).

The degree of hypoxemia depends on the level of occlusion (which determines magnitude of the shunt fraction) and the previous condition of the lungs.

HYPOVENTILATED/HYPOPERFUSED ALVEOLAR-CAPILLARY UNITS AS THE PRIMARY CAUSE OF HYPOXEMIA

Regional hypoventilation in diseased lungs. If airway changes cause the inspired air to be heterogeneously distributed to perfused alveolar-capillary units, an increased number of **units with low alveolar V/Q ratios and decreased P_AO_2** reduces the mean PO_2 of the blood leaving the lungs. **The P_aCO_2 may be increased**, but hypoxia-induced hyperventilation often keeps P_aCO_2 normal and even reduced in the initial phase.

Common causes of such changes may be

- Heterogeneously distributed bronchospasm and/or edema of the mucous membranes.
- Localized compression of small airways (e.g. interstitial edema).
- Remodeling of small airways by disease (chronic inflammatory processes).

Regional hypoperfusion in diseased lungs, where localized obstruction to alveolar perfusion leads to no (alveolar dead space) or reduced (very high V/Q ratios) blood flow to ventilated alveolar-capillary units. **P_aCO_2 may be increased if normal ventilation volumes are maintained**, in which case the **P_aO_2** also decrease. As hypoxemia and reflexes from lung tissue often cause hyperventilation, **P_aO_2 changes may be small** if P_aCO_2 is kept normal or reduced in the acute phase. In acute pulmonary *embolization* (see below), accompanying localized airway changes may lead to substantial P_aO_2 reductions and severe hypoxemia in some patients. Regional hypoperfusion may be caused by

- Macro-or micro-embolization with thromboembolic material, fat, air, etc.
- Thrombosis of pulmonary vessels
- Remodeling of pulmonary vessels secondary to PA hypertension or other diseases.

Simultaneous occlusion of airways and vessels supplying the same alveolar area.

If both airways and blood flow to the same alveolar areas are occluded simultaneously, neither shunt nor dead space develops. The total alveolar-capillary surface area available for gas exchange is, however, reduced, and the capacity for oxygenation of the blood during increased flow situations is limited. If larger areas of the lung vasculature are occluded or removed, increased vascular pressures in the remaining vessels may lead to increased strain on the right ventricle (139); possibly also hydrostatic edema in the pulmonary tissue supplied by the vessels that still are perfused (see below). Such considerations limit the amount of lung tissue that can be resected surgically (140).

HYPOXEMIA DUE TO INCREASED SHUNTING (V/Q = 0)

Fluid-filled alveoli are a common cause of increased intrapulmonary shunting. In most patients, the source of such fluid is plasma filtrated or leaked from the pulmonary circulation. There are two different mechanisms for creation of such edema:

- **Edema caused by increased transmural hydrostatic forces** (i.e. high intravascular pressures (common, see LV failure and others below) *or* low airway pressures (rare)). The edema fluid consists of plasma water with a low protein content; the fluid can be absorbed and the respiratory failure reversed within hours if the transvascular pressures can be normalized.

- **Edema caused by increased microvascular permeability** despite normal or even reduced transmural vascular pressures. The rate of fluid extravasation still changes, however, with the transvascular pressure. The edema fluid has a high protein content and resembles plasma, with gel-like properties if extravascular proteins participating in the coagulation cascade are activated. This type of edema is often accompanied by additional tissue changes induced by inflammatory processes (see ARDS below); re-absorbtion of the edema fluid usually takes days.

Very high hydrostatic pressures may damage the capillaries and lead to increased permeability of all parts of the blood; inhalation of gases with corrosive properties may also damage and destroy the alveolar-capillary units.

Rare, but dramatic and rapidly lethal, conditions where all the alveoli rapidly lose the ability to oxygenate the venous blood are

- **Non-ventilation** of the lungs (respiratory arrest *or* airway occlusion above the tracheal bifurcation, see above)).
- **Inhalation of asphyxiating gas**, i.e. the inhaled gas contains minuscule amounts of, or no, O_2.
- **Massive aspiration** of fluid into the airways, filling the alveoli.

In such conditions, hypoxemia becomes life-threatening within seconds to a few minutes, long before CO_2 accumulation and respiratory acidosis reach dangerous levels.

Direct inhibition of O_2 diffusion through the alveolar-capillary membrane was previously assumed to be an important cause of hypoxemia; it is probably a rare condition and occurs only at increased altitudes or during exercise in patients with chronic lung conditions associated with fibrosis (141).

PULMONARY EDEMA: FORMATION AND ETIOLOGIES

Edema fluid initially leaves the vascular space through the wall of extra-alveolar vessels and enters the interstitial tissue spaces. This **interstitial edema** may compress the small extra-alveolar airways passing through such spaces and lead to hypoventilation (low V/Q) of the alveoli situated distal to the compression. At this point, administration of supplementary O_2 may normalize the P_aO_2. If the pressure of the interstitial fluid increases further, edema fluid starts to fill the respiratory bronchioles (78, 142) and subsequently the alveoli, creating **alveolar edema.** This stage is accompanied by the classical signs of bubbling respiratory sounds and possible coughing-up of edema fluid. Edema formation caused by increased hydrostatic pressures starts where capillary pressures are highest, i.e. in the lowest part of the lungs (i.e. closest to the diaphragm when sitting up). High pulmonary vascular pressures resulting from failure of the left ventricle is the most common cause of hydrostatic pulmonary edema. As fluid-filled alveoli represent a shunt condition (V/Q = 0), the effect of O_2 administration at this stage is limited (see also Part 4-4, fig 4-29).

The exact capillary pressure when hydrostatic edema starts to develop is not known; in animal experiments, pulmonary edema develops at a mean capillary pressure of around 24 mmHg (143) *or* a left atrial pressure of 25 mmHg or above (144). As most of the resistance in the pulmonary vascular bed is situated pre-capillary (64), the pressure in the pulmonary artery can be higher than these before pressure in the capillaries reach a level where alveolar edema develops.

CONDITIONS WHERE PULMONARY EDEMA IS CAUSED BY INCREASED HYDROSTATIC PRESSURES

Hydrostatic edema and left ventricular failure.

Gravitational forces make the hydrostatic forces greatest in the lowest part of the lung; accordingly, the edema formation starts there in sitting patients but become more evenly distributed when supine. Reduced compliance of the lungs also increases the workload of the respiratory muscles; if hypoxemia reduces their O_2 supply, the risk of muscular fatigue and ventilation insufficiency increases.

Treatment that increase the mean airway pressures (PEEP, CPAP, IPPV, etc. - see Part 4-4) dilates the small airways and increases the mean size of acini and alveoli; this may increase the number of functioning alveolar-capillary units, augment the alveolar-capillary surface and improve oxygenation within minutes. Severe hypoxemia can then be avoided until treatment directed toward the LV circulatory failure (e.g. diuretics, preload/afterload reduction, inotropic support, and arrhythmia control) reduces edema formation and facilitates fluid resorption. Especially in left ventricular failure where increased resistance to ejection (increased afterload) induced by high blood pressure is a major component, treatment with a combination of vasodilator drugs and inotropic agents (Part 3-4) may reduce pulmonary edema formation within minutes.

If no improvement in oxygenation is seen after the institution of treatment directed at improving the LV failure, the efforts to improve the cardiac function have failed, *or* there are other factors in addition to LV failure that contribute to the development of shunting.

Hydrostatic edema due to sub-atmospheric airway pressure.

This type of hydrostatic edema is relatively rare and usually occurs as a consequence of maximal inspiratory efforts during severe obstruction of the upper airway. Such obstruction may be due to laryngospasm or an otherwise compromised airway after anesthesia (145), or as a result of disease (e.g. epiglottitis, croup, aspiration of foreign bodies). Compression of the trachea by goiters, tumors, etc. may also precipitate such edema. Healthy adolescents and adults can generate negative airway pressures of about 76 cmH_2O (≈56 mmHg) (women) and 107 cmH_2O (≈79 mmHg) (men) during inspiration when measured at mouth level (146); pressures *at least* as low as these can exist on the alveolar level during maximal inspiratory effort during total occlusion of the upper airways.

The simultaneously increased pressure in the pulmonary capillaries and decreased airway and tissue pressure increase the transvascular capillary pressure and favor increased fluid filtration out of the vessels, into the interstitial space, and further into the alveoli (147, 148).

Hydrostatic edema due to reduced number of open pulmonary vessels.

If a substantial percentage of the pulmonary vessels are severely narrowed or occluded, and the total blood flow through the pulmonary circulation is maintained or increased, the hydrostatic pressure in the remaining vessels must increase. Due to the high compliance of normal pulmonary vessels, a loss of close to 50% of the pulmonary vessels after surgically removal of one lung in animals have only a modest impact on pulmonary arterial pressures (149); also in otherwise healthy humans, pneumonectomy, or increased pulmonary blood flow due to atrial septum defect, do not necessarily lead to pulmonary hypertension (150). From a mechanical perspective, it has been calculated that around 55% of pulmonary vasculature must be occluded or resected

before pulmonary hypertension becomes a problem in patients if the remaining lung vasculature is essentially normal (151).

Pulmonary embolization as a cause of edema.

About 25-30% of the vasculature in a previously healthy vascular bed can be obstructed by pulmonary emboli before the resting mean hydrostatic pressures in the pulmonary artery rises to hypertensive levels (MPAP ≥ 25 mmHg, i.e. 5 mmHg above the upper normal limit) (152). The difference in consequences of eliminating part of the vessels by surgical means, and leaving them in a non-functional state after embolization with thromboembolic material, supports the assumption that chemical and reflex vasoconstriction exerts an important additional effect to the mechanical obstruction in pulmonary embolization, see also below.

Hypoxic and neurogenic vasoconstriction.

In addition to the mechanical obstruction caused by *major pulmonary emboli* (153), reflexes may increase resistance in other, still open, vessels. Hydrostatic edema may also be precipitated when alveolar hypoxia cause intense pulmonary vasoconstriction at **high altitudes** (154) or during massive sympathetic discharge, as when **neurogenic pulmonary edema** (155) increases the capillary pressures in the still perfused areas.

CONDITIONS WHERE THE EDEMA IS CAUSED BY INCREASED VASCULAR PERMEABILITY.

Inflammatory reactions, whether induced by microorganisms in the airways (pneumonia) *or* by blood-borne proinflammatory signal molecules (see below), may increase the microvascular vascular permeability in all organs. In the lungs, such permeability increase favors edema development even when transvascular pressures are normal or subnormal. This edema fluid contains a high concentration of plasma proteins, including proteins of the coagulation cascade, which accompanies the plasma fluid into the interstitium and alveoli. Due to the gel-like properties of such fluid (156), frothy edema fluid in the upper airways is unusual except for in rare instances with massive damage of the lung tissue. The viscous properties also make lymph drainage of extravasated fluid less efficient.

Increased permeability edema due to inflammatory reactions can roughly be divided (157, 158) into those resulting from

- **Lung tissue injury caused by microorganisms** (e.g. viruses, bacteria, fungi) **entering via the airways**, after which an inflammatory response is mounted **locally** in the affected part of the lungs (**intrapulmonary etiology**). Pro-inflammatory agents generated in the affected areas may, however, spill over into the blood and create inflammatory changes also in the rest of the body (fig. 4-22).
- **Lung tissue injury caused by proinflammatory agents released by diseased or damaged tissues distant from the lungs** (e.g. systemic infections, peritonitis, severe pancreatitis, major non-thoracic trauma – **extrapulmonary etiology**). Such agents, and leukocytes activated by the extrapulmonary processes, reach the lungs as blood-borne agents and create a diffuse inflammatory reaction (fig. 4-22, right).

In addition, similar pathologic changes can be elicited by

- **Lung contusion**, i.e. inflammatory changes induced by blunt external mechanical trauma to the lungs.

- **Inhalation of toxic** and/or **injurious agents** (e.g. aspirated fluids, inhaled gases, fumes, or aerosols). Inhalation of injurious fumes or gases (e.g. chloride, ammonia, nitrous gases, phosgene, and arsene) may cause airway irritation in low concentrations; severe inflammation and tissue damage develop, however, when the airways are exposed to higher concentrations. Inhaled agents with a high solubility in water exert their damaging effects mostly in the upper airways; those with lower solubility penetrate deep into the alveoli and may destroy the type 1 alveolar cells, denuding the pulmonary capillaries and favoring the development of alveolar edema (159, 160, 161), see also below.

Regardless of the triggering event, increased permeability edema is an important pathophysiological element in respiratory failure due to the condition classified as an **acute respiratory distress syndrome,** as described below.

Filling of alveoli with pus and cellular debris generated by infectious and inflammatory processes**,** or with **aspirated blood, gastric contents, or other fluids** have consequences for alveolar gas exchange similar to those of edema fluid.

THE ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is not a disease *per se*, but a syndrome characterized by acute diffuse alveolar damage leading to increased intrapulmonary shunting and pulmonary failure of varying severity. It is a blanket term for a heterogeneous group of conditions where the initial presentation, as well as timelines and pathological changes in pulmonary tissues, vary considerably. A patient with acute lung failure is defined as having ARDS if the clinical presentation and the gravity of pulmonary dysfunction satisfy certain criteria, and conditions leading to a purely hydrostatic edema can be ruled out (see definitions below). The inflammatory processes leading to pulmonary injury results from a wide variety of etiologies (162, 163). Other well-defined pulmonary diseases may, how-ever, masquerade as ARDS when the progression of the disease is rapid (164).

Despite the heterogeneous nature of precipitating conditions as well as the initial clinical presentation, the main histological picture in the acute phase is surprisingly similar and consists of

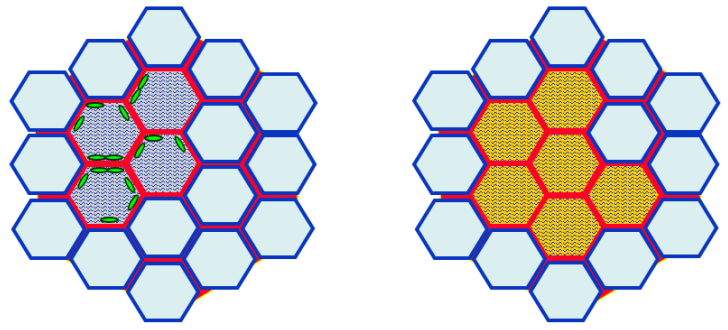

Figure 4-22. *Inflammatory alveolar edema can be caused by pro-inflammatory agents released from invading microorganisms locally (left), or by agents released from infections or damaged tissue elsewhere in the body (right).*

- **Severe damage to a substantial number of alveolar-capillary units.**
- **Interstitial and alveolar edema**, independent of whether the hydrostatic pressures in the pulmonary microcirculation are increased or not (Non-cardiac pulmonary edema).
- **Vascular aggregation and tissue infiltration of leukocytes**, mainly polymorphonuclear neutrophil granulocytes (PMN).

Additional signs of structural tissue damage and microvascular thrombosis are found at autopsy (see below).

Development of the ARDS concept.

The connection between acute hypoxemia and pneumonia or cardiac failure has been recognized for more than a century (165, 166). The occurrence of seemingly unexplained severe pulmonary failure after surgery, civilian trauma, or combat wounds has also been recognized for a similar period. The *etiology* of this latter type of respiratory failure was a topic for discussion for a long time; at different periods the condition was described as "post-operative massive collapse of the lungs (167), "acute massive collapse of the lungs", "active lobar collapse" (168), "shock lung", "wet lung", "Da Nan lung" (169), etc. Already during World War II, the value of assisting inspiration in such patients and keeping the airway pressures increased *above* ambient pressure was recognized (170). Positive pressure ventilators were, however, not commonly available at that time (171), such treatment coiuld therefore not be offered to patients in general.

Regardless of the initiating events described above, the anatomical and pathophysiological changes in the lungs of patients developing severe acute respiratory failure are surprisingly similar. The lungs of those who die early show vascular congestion, severe interstitial, alveolar edema, and focal atelectasis; vascular thrombi, fat emboli, bleeding, fibrin deposits, and hyaline membranes (consisting of dead cells and proteins) were also commonly found at autopsy (172).

The ARDS designation for such pulmonary failure was first used by Ashbaugh and colleagues in 1967 (173). After treating a group of adult patients with severe, diffuse lung failure of various etiologies and with high mortality, they coined the designation Adult Respiratory Distress Syndrome (**ARDS**). These patients had a reduced amount of surfactant in the lungs, at autopsy, the pulmonary changes were similar to those described above. The authors also noted a positive effect of applying Positive End Expiratory Pressure (**PEEP)** on oxygenation of the blood (174, 175). The designation "Adult" (originally intended to distinguish it from the Infant Respiratory Distress Syndrome (IRDS)), was replaced by "Acute" during the 90-ties, keeping the abbreviation unchanged; ARDS thus came to mean the Acute Respiratory Distress Syndrome.

The importance of activation of the immune system, and subsequent inflammation for the development of this type of lung dysfunction was first indicated by the work of a research group at the University of Minnesota in the 1970-ties. They found that activation of the complement system in the blood, which stimulated and aggregated circulating polymorphonuclear granulocytes (PMN) (176), had negative, but reversible, effects on arterial oxygenation (177, 178) and induced increased microvascular permeability in the lungs (179). Activated PMNs have a considerable destructive capacity, foremost through their capability to generate reactive oxygen intermediates (ROI) and to release tissue-degrading enzymes (180, 181). These weapons, which are a part of the innate defense against invading micro-organisms, can also destroy and damage autologous tissue (182, 183).

The role of the innate immune system in ARDS development came into focus; the findings of the University of Minnesota group inspired a multitude of research projects into the connections between the release of pro-inflammatory agents, changes in leukocyte function, and pulmonary dysfunction. Subsequent research has supported the role of PMN and the immune system in ARDS development. The inflammatory processes leading to ARDS development, however, are much more complex than just stimulation of PMNs by activated complement (184, 185), and that release of pro-inflammatory cytokines (see also Part 2-4) plays a crucial role.

Past and present definitions of ARDS.

The inflammatory processes leading to ARDS may roughly be divided into **intrapulmonary** and **extrapulmonary** etiologies (157, 158, 186), see above and fig. 4-22.

As a general rule, the damage process in patients with the former type of lung injury may start with damage to the alveolar epithelium while endothelial damage may be the initiating process in the latter (156). In the early phase of ARDS, there may be some differences in morphological aspects and respiratory mechanics between the two groups, these differences do not seem to result in differences in mortality. Early definitions of ARDS included reduced lung compliance in the description of the syndrome (187); as this may not be manifest during the initial stage of disease, compliance reduction has not been included in the two latest definitions (see below).

To facilitate the grouping of disease severity in connection with scientific investigations of prognosis and treatment effects, the less serious variant of ARDS was termed *Acute Lung Injury* (**ALI)** as a result of a consensus conference in 1994 (186). The latter term was discarded during a new consensus conference in 2011 (188); in the intervening years, however, thousands of scientific papers using this term for severity classification were published.

The current definition of ARDS (the "**Berlin definition**") is a respiratory failure that

- Occurs **within one week** of a known clinical insult *or* new or worsening respiratory symptoms
- Show **bilateral opacities** not fully explained by effusions, lobar/lung collapse, or nodules on chest imaging *and*
- Cause **pulmonary edema** that is not fully explained by cardiac failure or fluid overload.

Three **degrees of severity** are defined, based on the impairment of gas exchange as measured by the **P_aO_2/F_iO_2 ratio** with the application of CPAP/PEEP ≥ 5 cmH_2O;

- **Mild ARDS: 26.7 kPa (200 mmHg) < P_aO_2/F_iO_2 ratio ≤ 40 kPa (300 mmHg)**; e.g. a P_aO_2 of 10 kPa (75 mmHg) with a F_iO_2 between 0.25 and 0.375 *or* a P_aO_2 of 8 kPa (60 mmHg) with a F_iO_2 between 0.20 and 0.30 satisfies the criteria.
- **Moderate ARDS: 13.3 kPa (100 mmHg) < P_aO_2/F_iO_2 ratio ≤ 26.7 kPa (200 mmHg),** e.g. a P_aO_2 of 10 kPa (75 mmHg) with a F_iO_2 between 0.375 and 0.75 *or* a P_aO_2 of 8 kPa (60 mmHg) with a F_iO_2 between 0.30 and 0.60 satisfies the criteria.
- **Severe ARDS: 13.3 kPa (100 mmHg) ≤ P_aO_2/F_iO_2 ratio,** i.e. a P_aO_2 of 10 kPa (75 mmHg) with a F_iO_2 above 0.75 *or* a P_aO_2 of 8 kPa (60 mmHg) with a F_iO_2 above 0.60 satisfies the criteria.

For comparison, the ratio for **normal lungs** when breathing room air is: 13.3 kPa/0.209 = **63.6 kPa** *or* **478.5 mmHg**. The **previous definition of ALI** *did not specify the use of* CPAP or PEEP but was otherwise similar to the current definition of **mild ARDS**. The previous **1984 definition of ARDS** encompasses both moderate *and* severe ARDS according to the current definition.

The natural course of ARDS.

With the advent of modern intensive medical care, ARDS patients in general survive longer than before. Only about 10-15% of those who die succumb to hypoxemia *per se* (189, 190); with the treatment and resources available in the ICUs of industrialized countries today, the majority of the patients die of multiorgan failure. Most investigators report the mean time of death in non-survivors as 5-7 days after diagnosis (189, 191); the cause of death is, however, heavily influenced by the precipitating cause as well as therapeutic strategies (192). ARDS has been viewed

as the pulmonary manifestation of a systemic inflammatory syndrome that affects most of the body's organs; as all the blood passes through the lungs, inflammatory mediators released by a lung will spread to the whole body.

In most patients today, the progression of the condition consists of *three phases of disease* plus *a resolution phase*. These are categorized (193, 194, 195) as

- **The exudative phase**, which is dominated by diffuse alveolar damage characterized by edema (most prominent first 2-3 days), accumulation of neutrophil granulocytes (PMN), hyaline membranes in the alveolar space, and endothelial/epithelial damage. The endothelial surface changes from an anticoagulant to a procoagulant state (196) with consumption of platelets. This phase lasts for a week or less after diagnosis.
- **Proliferative phase**, where edema and PMN accumulation are still evident, atelectasis is widespread and fibroblast infiltration has started. This phase is usually most prominent between the first and second week after diagnosis.
- **The fibrotic phase**, where the PMN has been replaced by lymphocytes and macrophages, and fibrosis and proliferation of type II alveolar cells are the dominating picture. This phase is commonly predominant 10-14 days after diagnosis.
- **Resolution phase**, in which relative normalization of lung architecture and regression of the fibrosis is found in survivors.

As the etiology is heterogeneous and the development and resolution of lung failure in individual patients proceed at different speeds, a considerable overlap exists between the phases. During times and conditions where treatment with positive pressure ventilation with increased end-expiratory airway pressures was not generally available, more patients probably died from generalized hypoxemia within a few days after initiation of symptoms. The pathological changes found at the time of biopsy/autopsy can be expected to vary according to the phase above, and to differ from earlier descriptions of patients dying in the early stage of disease after developing "shock lung".

In some patients, a *resolution phase does not occur*. Even if gas exchange and blood oxygenation improve, an aggravated fibrotic response results in lungs with a compliance that may be too low for the patient to maintain adequate tidal volumes without mechanical assistance. In this group of patients, mortality is considerably higher than in those with little or no fibrosis (197, 198).

Ventilator-induced lung injury (VILI).

The term VILI encompasses all types of injury to the lungs related to treatment with positive pressure ventilation. The occurrence of pneumothorax in patients ventilated with high airway pressures has long been recognized (199); other negative effects on the lung tissue have come to the forefront during the recent decades after the realization that utilizing high airway pressures, large tidal volumes, or both, are independent sources of additional lung damage. The concept of VILI is intimately connected with positive pressure ventilation in ARDS patients; implicit in this concept is that ventilating the lungs of such patients with low pressures and tidal volumes can protect the lungs from additional damage. The modern concept of VILI (reviewed in refs. 200, 201) thus focuses on ventilating the lungs in a mode that minimizes such additional damage to the lungs.

Already in the 1970-ties, positive pressure ventilation of rodents (which have a much more compliant chest wall than adult humans) with peak pressures of 45 cmH_2O was, not unsurprisingly,

shown to induce massive lung damage (202). Initially thought to be a pressure-induced phenomenon ("barotrauma"), further research indicated that it was the excessive increase in lung *volumes and tissue expansion*, and not the pressures *per se*, that induced the damage (203). Considering the fragile nature of the lung tissue, the destructive effect of massive tissue overextension ("volutrauma") is easy to understand. In addition, continuous closing and opening of alveoli in diseased lungs have an independent damaging effect ("Atelectrauma" (204)), these types of lung injury can be modified by the application of positive end-expiratory pressure.

The tissue overextension necessary to damage the lungs probably differs between spontaneous and positive pressure ventilation. Maximal tidal volumes in healthy adults are around 4-5 liters (see fig. 4-6), which in a 75 kg person with a normal build is equivalent to around 60-70 ml/kg vs around 7 ml/kg during normal ventilation in a resting person. In healthy athletes, the tidal volumes during maximal exertion are close to 3 liters (i.e. around 40 ml/kg in a 75 kg person (205); during a marathon run for more than 2 hours, tidal volumes are 3-4 times normal (206), i.e. 21-28 ml/kg. The tolerance of a healthy lung to tissue stretch during spontaneous ventilation with high tidal volumes is thus different from positive pressure ventilation of a diseased lung (see tidal volumes, Part 4-4), the duration of exposure to high V_T's may be an important factor.

In many patients with severe ARDS, only parts of the lungs are available for ventilation; ventilating such lungs with tidal volumes suitable for healthy lungs could lead to overextension damage to the still-ventilated part of the lungs. Continuous stretching and relaxing of inflamed tissue may keep cells involved in the inflammatory reaction (macrophages, granulocytes) in a state of permanent activation (207, 208, 209).

A large study, conducted by the research group ARDS Network, concluded that ARDS patients, ventilated with relatively normal tidal volumes, i.e. 6 ml/kg, did better than those ventilated with volumes twice as high (18). The study has been criticized for choosing a tidal volume higher (i.e. 12 ml/kg) than what was commonly used at the time of the study (210) for comparison purposes. Nevertheless, a consensus has evolved that one of the ways to minimize lung injury is to restrict the tidal volumes to 6-8 ml/kg, possibly lower in severe ARDS, and always use PEEP (no consensus as to how high, but *at least* 5 cmH_2O) during mechanical ventilation. Some authors have hypothesized that the risk of VILI can be diminished by ventilating with even lower volumes (e.g. 3 ml/kg (211)); as the anatomical dead space volume amounts to about 2 ml/kg (lower in intubated patients), this may lead to severe hypercarbia and reduce the amount of O_2 entering the alveolar space with each breath. A recent study did not find any advantage of a 4 ml/kg tidal volume strategy vs a 6 ml/kg strategy in non-ARDS patients (212). Except for the study of the ARDS network mentioned above, there is little evidence that VILI can be avoided by employing one "ideal" ventilation mode suitable for all ventilated patients, or that development of VILI is a separate risk factor for mortality in ARDS patients (213).

OTHER CAUSES OF NON-CARDIAC ACUTE RESPIRATORY FAILURE

Acute obstruction or occlusion of pulmonary vessels.

Partial obstruction of a branch of the pulmonary arterial vasculature changes the V/Q ratio of all alveoli perfused exclusively with blood from that branch into a high V/Q area; if there is a *total* vascular occlusion, *all* such alveoli become an alveolar dead space, with a V/Q = ∞.

Partial vascular obstruction or occlusion can be a result of

- **Pulmonary thromboembolism,** where material released from thrombosis in deep veins or the right heart lodge in the pulmonary vessels. This is the most common cause of pulmonary embolism.
- **Fat embolism,** where the fat is released from bone marrow, usually a result of trauma involving fractured bones, but fat droplets may also be created by other mechanisms.
- **Air Embolism,** where air bubbles are created during a rapid decompression, air sucked into damaged veins, or iatrogenic, caused by instrumentation of veins and tissue in general.
- **Emboli** consisting of **necrotic or infected tissue material, exogenous material, or amniotic fluid** can be released into the venous blood and follow the bloodstream to the pulmonary circulation.
- **Rigid erythrocytes in sickle cell disease**, where aggregates of abnormal cells may create widespread microembolization in the lungs.
- **Microthrombosis** are commonly found in ARDS lungs, where inflammatory changes make the endothelium pro-thrombotic.
- **Hypoxic vasoconstriction** (a physiologic defense mechanism if only regional, (see previously), but may be dangerous if generalized (e.g. at high altitudes)).

Pulmonary thromboembolism: the clinical presentation.

Pulmonary thromboembolism **(PE)** is by far the most common type of acute pulmonary vascular obstruction. The initial symptoms of a pulmonary embolic incident depend primarily on the extent of the embolization *per se*, but also on whether a previous cardiopulmonary disease is present (153). Almost all patients (97% in one study (214)) have either *dyspnea*, *tachypnea,* or *pleuritic pain*, *hemoptysis* was also common. In the same study, a moderate *reduction in* P_aO_2 (to below 10.7 kPa or 80 mmHg) was seen in 74% of the patients (see Blood gases below). In *massive embolization*, circulatory instability or shock is caused by a combination of right ventricular afterload increase and failure of left ventricular diastolic filling. In circulatory stable patients, mortality is moderate (about 4.5 % (215) to 7.5% (216, 217), while unstable circulation is associated with mortality of about 25% (218) or more. Mortality in massive pulmonary embolization is usually not due to hypoxemia *alone*, but to a combination of hypoxemia and circulatory failure, see Part 3-3. The majority of those who die, do so within the first 2.5 hours after the start of symptoms, which may explain why a definite diagnosis of PE *before death* in such patients is made in only 30% of those who succumb (219).

Blood gas changes in pulmonary embolism.

From a theoretical standpoint, PE with the creation of low V/Q or V/Q = ∞ areas could lead to increased P_aCO_2 with only a modest impact on blood oxygenation; indeed, in one study, about 25% of patients with angiographically documented pulmonary thromboembolism had a relatively normal P_aO_2 (220). Even if the calculated alveolar dead space is increased (221), patients with clinically important pulmonary embolisms usually present with a normal or decreased P_aCO_2 due to compensatory hyperventilation (222).

As a reduction in alveolar PCO_2 is expected to increase the PO_2, it has been suggested that the P_AO_2-P_aO_2 gradient is a more sensitive parameter than P_aO_2 alone in patients with pulmonary emboli. In one study, 14% of the patients did not, however, show a clinically significant increase in this parameter (218). Part of the stimulus leading to hyperventilation may be due to hypox-

emia; additional mechanisms, like activation of receptors in the pulmonary tissue, probably participate in this response as correction of hypoxemia by increasing the F_iO_2 does not necessarily stop the hyperventilation (223).

Even if P_aO_2 is not reduced in *all* patients, a large proportion of PE patients present with hypoxemia, irrespective of the P_aCO_2 level (224). Several mechanisms may participate in the gas exchange derangement:

- Reductions of the alveolar V/Q in areas not directly affected by the embolization (e.g. hydrostatic edema (see above), hyperperfusion of remaining open vessels (diffusion limitation), and bronchoconstriction (reflexes, signal molecules from affected tissue). In patients where 50% or more of the vessels are occluded, edema in areas with non-occluded vasculature could cause hypoxemia due to high-pressure edema (see edema formation above). Such edema cannot, however, be the major mechanism of V/Q disturbances in most PE patients, as P_aO_2 can be reduced when only 13% of the pulmonary vessels are occluded (152). Additional explanations, other than alveolar edema, must be important for V/Q abnormalities and hypoxemia in PE patients. Several factors can be involved in the development of low V/Q areas in PE, among these reduced ventilation in local areas close to the emboli induced by serotonin and Thromboxane A_2 (225, 226, 227), and reflex constriction of both airways and pulmonary vessels (151).
- Increased diastolic right-to-left shunts through a patent foramen ovale, due to increased pressures on the right side and decreased on the left side of the heart.
- Amplification of the effect of low V/Q and shunt areas by a reduced S_vO_2 *if* the right ventricle fails due to high PA vascular resistance and low C.O. reduces the DO_2.

Embolism caused by material other than thromboembolic may cause additional effects on the V/Q ratio. Air microembolization has been used in animal experiments to create an ARDS-like syndrome with increased vascular permeability (228), fat emboli may, in addition to occlusion of vessels, also induce an ARDS-type inflammatory state (229, 230).

Pulmonary vascular thrombosis

Thromboembolism — macro- and micro-thrombi in the pulmonary vessels - is a common finding in an autopsy of patients dying from the ARDS (231). Whether these are purely a result of endothelial dysfunction or also represent organized material from venous thrombosis is difficult to ascertain.

Effect of sickle cell disease in the lungs.

In this inherited disease, a genetic change in the Hb molecules makes them stiff and non-deformable in the presence of a low PO_2 (i.e. in the unsaturated state of Hb). The stiff erythrocytes may aggregate and lodge in the microcirculation everywhere, also in the small pulmonary vessels (232). Reductions in blood PO_2 and increased pulmonary vasoconstriction may then result in a vicious circle where increased hypoxemia leads to increased sickling and diffuse microembolization in the lungs (Chest syndrome, see Part 2-3) and elsewhere in the body.

Embolization with necrotic or infected tissue material, exogenous material, or amniotic fluid.

Any type of material that can make its way into the venous circulation may follow the bloodstream to the lungs. Embolization with amniotic fluid is special, as it can only occur during pregnancy, it is a relatively rare disease (occurring in somewhere between 1:13 000 to 1:52 600 deliveries).

The majority of cases occur during the period from *two hours before* to *four hours after* delivery. The mortality is high but varies substantially between various publications (11% to 89%) (233). It is important to be aware of this condition if sudden non-hypovolemic shock accompanied by respiratory symptoms occurs in connection with spontaneous or cesarean delivery. The symptoms may be due to the mechanical effects of embolization of material *per se*, but immunological reactions and proinflammatory material in the fluid may also contribute to the severity of the reaction (234).

Drowning.

In drowning, cardiac arrest is secondary to severe hypoxemia in most persons. Inhalation of water during submersion has several effects. In addition to filling alveolar areas with salt or fresh water, edema may be created by intense inspiration attempts if laryngospasm has caused a total occlusion of the upper airways. The intense muscular activity during attempts to get to the surface increases O_2 consumption, which aggravate the hypoxemia.

In those rescued before cardiac arrest occurs, or are resuscitated successfully, an ARDS-like picture may exist for a limited time. Fluid in the alveoli creates shunts, and aspirated fluid flushes out surfactant leading to atelectasis. Bronchial spasms in response to airway irritation induce local V/Q decrease. The aspirated water fluid is, however, rapidly absorbed from the alveoli, and the pulmonary function usually improves within hours if no massive aspiration of stomach contents or water contaminants have occurred during the drowning episode (235, 236).

Inhalation/ingestion of toxic and corrosive agents.

Any gas or fluid that irritates and/or damages the airway mucosa (e.g. ingestion of corrosive fluids, inhalation of fire smoke, or toxic gases) may cause obstruction or occlusion of upper airways and damage peripheral lung tissue (i.e. the small airways and alveolar-capillary units).

The heat from fire smoke usually causes damage only to the upper airways; the reactive edema developing here may lead to severe edema and airway obstruction necessitating intubation or tracheostomy. In addition, fire smoke also contains particulate matter which may obstruct both large and smaller airways through reactive edema of mucus membranes and aggregates of soot particles filling the lumen of the airways (237, 238). In addition, fire smoke may contain toxic gases like carbon monoxide (239, 240) and hydrogen cyanide (241); the effects of these may aggravate the effects of hypoxemia.

Ingestion of corrosive fluids usually also causes damage only to the upper airways (242, 243). If aspirated to the airways, they cause a chemical injury to the more distal parts of the lung.

The most common agents that may reduce the pulmonary gas exchange capacity temporarily or permanently are inhalation of various Toxic Industrial Chemicals (TICs). Chemicals that have been synthetized with the intention to harm or incapacitate (Chemical War Agents – CWA) have been used in warfare and as weapons of mass damage/destruction (see refs. 159, 244, 245, 246 for an overview of the more common agents and their effects). Some gases (e.g. ammonia, hydrogen chloride, sulfur dioxide) react rapidly with the fluid lining of the mucosa in the upper airways; their damage is therefore mostly confined to the upper airways, and airway obstruction due to edema is the main mechanism of damage. Others (e.g. phosgene, nitrous oxides, mustard gas) react more slowly and reach the peripheral lung tissue, where they damage the alveolar-capillary units and create increased permeability edema; i.e. ARDS-type damage.

Damage and destruction of lung tissue by mechanical forces.

Barotrauma is caused when high airway pressures over-distend the airways and cause tissue rupture; usually in the peripheral part of the lung. **Direct mechanical trauma** to the chest of any type (e.g. traffic accidents, falls, and crush injuries) can injure the lungs; such types of trauma are usually accompanied by visible outer injuries. **Blast injuries** caused by explosions, where a pressure wave travels through the thoracic wall and into the lung tissue, can lead to severe lung damage in the absence of external signs of trauma (247). A wide range of lung damage may result from thoracic trauma (e.g. lung contusion, multiple rib fractures, lung lacerations, pneumothorax, and hemothorax).

Decompression injuries are caused by a rapid expansion of gas in the peripheral airways and blood due to a sudden reduction of external pressures (e.g. rapid ascent from diving, sudden decompression).

- **Pneumothorax.** A sudden expansion of gas in the airways may damage the lung tissue and small airways; a common complication of this is small lacerations leading to a pneumothorax (248) which again may lead to rapid oxygenation failure (see above).
- **Gas emboli.** A rapid reduction in ambient pressure (decompression) may cause the gases (usually nitrogen gas) dissolved in the blood to expand and create bubbles, which then obstruct small branches of the pulmonary artery and acts as gas emboli.

Mechanical impediment of lung expansion.

Pleural accumulation of air (pneumothorax) or fluid.

Intrapleural air, blood (hemothorax), effusions (pleura fluid), *or* pus (in pleuritis) may occupy part of the intrathoracic volume (fig. 4-23). The space occupied by air or fluid reduces the lung volume and thus the alveolar gas space; the diameter of alveoli and small peripheral airways decreases and may lead to local hypoventilation and atelectasis. The impact on pulmonary gas exchange *per se* is primarily determined by how much the lung volume decreases. Increases in the intrathoracic pressure may also impede cardiac diastolic filling and reduce the C.O. This may reduce the DO_2 further, a fall of S_vO_2 may aggravate the hypoxemia.

Low-pressure pneumothorax arises when air enters the pleural space and breaks the hygroscopic seal between the thoracic and pulmonary pleural blades. Depending on the volume of air, the effect may range from a small retraction of the lungs (i.e. 1-2 cm) from the thoracic wall with modest effects on gas exchange to total lung collapse with the creation of a major shunt (fig. 4-23).

Air can enter the pleural space through two mechanisms

- Via the airways (the most common mechanism, where spontaneous or traumatic damage to the lung tissue on the lung surface creates communication between airways and pleural space). Most spontaneously breathing patients with pneumothorax have at least one costal fracture (249).
- Via damage to the thoracic wall (which usually is combined with lung tissue damage in penetrating trauma), or iatrogenic procedures which may be intentional (thoracic surgery) or accidental (puncture of the lung during placement of central lines). Intentional creation of pneumothorax was also used for the treatment of cavernous tuberculosis before effective antibiotics became available (250).

During spontaneous breathing, the negative pressure exerted within the intrapleural space during inspiration actively sucks air into the pleural space; as expiration is caused by the passive recoil of the lung tissue, the airway pressure is higher than the atmospheric during expiration and the escaped air does not return to the airways.

Positive-pressure pneumothorax (fig. 4-23C).

If lesions of the lung tissue or in the thoracic wall create a one-way flap valve, the air is sucked into the thoracic cage with each spontaneous inspiration, but cannot exit. The air volume may increase progressively; increased respiratory distress intensify the force of inspiratory muscles and thus the negative intrapleural pressure which sucks even more air into the pleural space. A positive pressure pneumothorax may result, with the collapse of the lung on the affected side and compression of the cardiac chambers and vessels of the central circulation and a low cardiac preload.

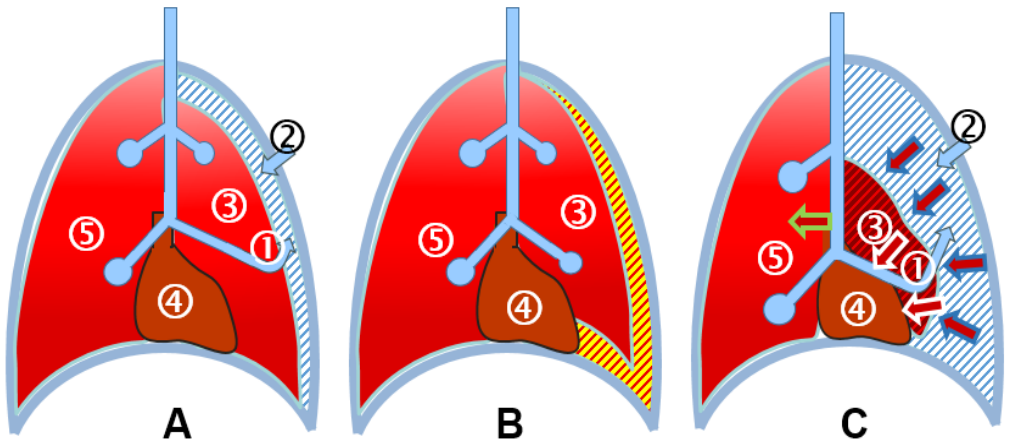

Figure 4-23. *Conditions where intrathoracic accumulation of air* (**A** and **C**) *or fluid* (**B**) *reduce the area available for alveolar air*. **A**. *Pneumothorax of moderate degree, where air enters the interpleural space through damage to the lung surface* ① *or thoracic wall* ②. *The volume of the affected lung* ③ *is reduced, the pressures outside the heart* ④ *is close to normal and the function of the other lung* ⑤ *remains relatively normal. The effect on* P_aO_2 *and* DO_2 *are modest.* **B.** *When the interpleural space is filled with fluid, the lungs float on top of the fluid; otherwise, the effects on* P_aO_2 *and* DO_2 *are modest.*
C. *If the lesion* (① or ②) *create a flap, functioning as a one-way valve, a positive pressure may build up in the intrapleural space (positive pressure pneumothorax). The lung* ③ *become compressed and dysfunctional, positive pressure outside the heart reduce end-diastolic filling* ④ *and the other lung* ⑤ *also becomes compressed as the mediastinum shifts.*

In patients who are being *ventilated with positive pressure ventilation*, a positive pressure pneumothorax may develop rapidly and become life-threatening within minutes. A plain frontal X-ray often divulges the diagnosis; it is, however, important to be aware of the limitations of such X-rays for detecting a frontal or a basal pneumothorax. Such localizations are more common in patients with previous lesions, where scar tissue anchor the lungs to the lateral chest wall.

In **hemothorax,** bleeding from injured lung tissue or vessels traversing the pleural space fills up part of the intrapleural space. In **pleural effusion,** inflammatory processes increase in vascular permeability *or* a generalized increase in venous pressures due to right-sided cardiac dysfunction increase the extravasation of fluid may cause fluid to accumulate intrapleurally.

In opposition to the situation in pneumothorax, where the air accumulates *above* the lungs, the lung tissue *floats* atop a layer of blood or effusive fluid. In practical terms, this means that the orifice of drains placed to evacuate air in a pneumothorax should be placed in the upper, apical part of the thoracic cage, while it should be placed as low as possible when evacuation of fluid is the goal.

Similar, but less dramatic, effects on the lungs and ventilation may be caused by **intraabdominal processes that interfere with diaphragmatic excursions** (e.g. extreme obesity, large volumes of ascites, bowel dysfunction with the accumulation of large volumes of air).

Traumatic deformities of the thoracic cage (e.g. flail chest) impede ventilation both through mechanical effects and pain on ventilation. In addition, the trauma to the thorax may have damaged the underlying lung tissue, aggravating the negative effects of hypoventilation.

CHRONIC RESPIRATORY DISEASE (CRD)

Chronic respiratory diseases (also called chronic lung disease) are a heterogeneous group of conditions where chronic inflammation, provoked by environmental and/or hereditary conditions, causes progressive and irreversible damage to airways and/or lung tissue. In a subset of patients, the primary problem is a permanent limitation of ventilation capacity and secretion elimination due to central nervous or neuromuscular diseases, with secondary changes in lung tissue. Regardless of etiology, tissue destruction, scarring, and deformation of small airways lead to progressive *increases in airway resistance*, *loss of elastic recoil* of the lung tissue, and development of *inhomogeneous V/Q distribution* over months to years.

In the early phase of the disease, symptoms at rest may be mild but become more accentuated during physical activity; when the disease process reaches an advanced state, the patients fulfill the criteria for respiratory failure at rest. A slow progression of the disease may be interrupted by acute exacerbations; in some patients, especially those with *asthma* (see below), such episodes may precipitate life-threatening hypoxemia.

In opposition to acute respiratory failure, where intrapulmonary shunting is the most common pathology, the stable phase of chronic lung disease is primarily characterized by heterogeneous alveolar ventilation where large numbers of alveoli have either a very low, or very high, V/Q ratio. The hypoxemia in such patients is therefore often considerably decreased or abolished in response to a modest increase in F_iO_2. In many patients, the number of alveoli, and thus also the total alveolar-capillary surface, is reduced (emphysema), making the excretion of CO_2 less efficient and resulting in increased hypercarbia.

Traditionally, patients with CRD have been divided into those where the symptoms primarily were characterized by either airway obstruction (*obstructive diseases*) *or* restriction of lung tissue and/or the thoracic cage expansion (*restrictive diseases*).

Obstructive diseases, where the main problem is increased airway resistance that most often represent a problem during expiration (e.g. chronic obstructive pulmonary disease, asthma). Obstruction may also be a problem during inspiration (e.g. asthma, extrathoracic tracheomalacia). End inspiratory gas volumes in the lungs (FRC) are usually normal or increased; the expiratory flow rate is, however, substantially reduced.

Restrictive diseases, where the main problem is a decreased ability to inhale sufficient volumes of air due to reduced lung compliance (e.g. inflammation, fibrosis, loss of functioning lung tissue), limited thoracic expansion (e.g. kyphoscoliosis, circular thoracic burns), or limited lung

expansion due to space-occupying conditions (e.g. pneumothorax, hemothorax/pleural effusions, extreme obesity). TLC is often, but not always, reduced while maximal breathing capacity (MBC, also called maximal voluntary ventilation – MVV) and expiratory gas flow, relative to TLC, are preserved during the earlier phase of the disease.

Changes in central nervous or neuromuscular function. A rarer subgroup of diseases are those where a loss of respiratory muscle strength is the primary cause of respiratory failure; some are subacute and partly reversible with appropriate therapy (e.g. myasthenia gravis, Guillain–Barré syndrome, and poliomyelitis), while others are slowly progressive irrespective of therapy (e.g. amyotrophic lateral sclerosis, Duchenne's muscular dystrophy). Such conditions also reduce TLC and tidal volumes; although etiologically different from the causes above; such diseases are often categorized as a type of restrictive disease. Hypoventilation increases P_aCO_2; the tendency to atelectasis and reduced ability to eliminate secretions leads to recurrent infections which over time cause structural damage to the lung tissue.

Both clinical presentation and the degree of gas exchange deterioration depend on whether the patients are in an early, intermediate, advanced, or terminal state of the disease. It can sometimes be difficult to decide whether a worsening of symptoms represents a *progression of the disease or* an *exacerbation* caused by microorganisms, inhaled agents, or environmental changes.

Even if there is a substantial overlap as to the pathological as well as pathophysiological consequences in the more advanced state of disease, CLD is usually divided into four major categories

- **Chronic obstructive pulmonary disease (COPD),** includes chronic bronchitis and emphysema and usually represents a slowly progressive disease in adults.
- **Asthma,** which involves a chronic state of airway inflammation; usually starts early in childhood; some patients may have severe, life-threatening, exacerbations (asthma attacks).
- **Interstitial lung disease and lung fibrosis,** may develop in response to inhaled material or be due to autoimmune disease or inherited factors and usually starts in adults.
- **Cystic fibrosis (CF),** is due to an inherited defect in the excretion of fluid by the airway epithelial cells; symptoms usually become obvious in early childhood.

The two former conditions are by far the most common, the third and fourth much rarer. While patients in all four categories exhibit some degree of hypoxemia, hypercarbia is most common in COPD and advanced stages of CF (251). Some infectious diseases also cause chronic and irreversible pulmonary dysfunction; **tuberculosis** (see below) is probably the most widespread of these.

Chronic obstructive pulmonary disease (COPD).

COPD is characterized by chronic obstruction of small airways, increased mucus production, and a state of chronic airway inflammation. It is an umbrella term for lung diseases previously classified as **chronic bronchitis** or pulmonary **emphysema**. The rationale for using a common designation for both conditions is that, in the more advanced state of disease, the lungs exhibit changes compatible with both bronchitis and emphysema (252), see fig. 4-24.

In most patients, the chronic inflammatory state is provoked by inhalation of irritating agents; tobacco smoking is a common culprit, but many environmental agents may also provoke a chronic inflammatory state. The pulmonary changes progress slowly, in most patients, the respiratory problems do not reach a stage where the diagnosis is established until the patients are in their fifties or older (253). In a subgroup of patients with hereditary dysfunction of production

of the enzyme alpha-1 antitrypsin, which normally protects against the effect of PMN elastase in the lungs, pulmonary emphysema may occur already at the age of 30 to 40 years (254, 255).

Chronic bronchitis leads to structural changes in the small airways, including

- Narrowing of small airways (peribronchial fibrosis, edematous epithelium).
- Hypertrophy of smooth airway muscle and connective tissue.
- Excessive mucus production and reduced ciliary function.

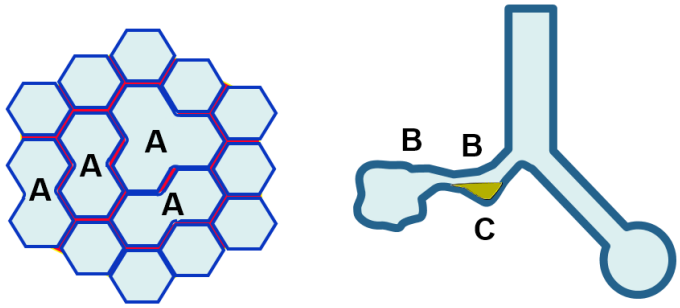

Figure 4-24. *Airway changes in COPD patients. The destruction of alveolar walls and their vascular supply* (**A**) *are typical empysematous changes. Scarred and narrow small airways* (**B**) *which cause hetergenous alveolar ventilation, and local dilatations (bronciectasies)* (**C**) *which functions as reservoirs for infectious material, are typical changes in chronic bronchitis.*

In addition, **bronchiectasis** (i.e. abnormally widening, often saccular, of bronchi) may develop, these act as reservoirs for infected mucus and cause further inflammatory damage (reviewed in refs. 256, 257).

The affection of small airways results in inhomogeneous ventilation, areas of reduced ventilation with reduced O_2 supply, and widespread low V/Q conditions result in reduced P_aO_2 and increased P_AO_2-P_aO_2 difference, progressing to hypoxemia.

Emphysema is another type of structural change in the pulmonary tissue, with wide-spread destruction of alveolar septa and sometimes of complete acini. The destruction is caused by proteases (primarily elastase) released by chronically activated PMNs and results in

- Reduced alveolar-capillary interface area (i.e. the gas exchange interface), creating increased alveolar dead space and high V/Q areas where perfusion is reduced or eliminated.
- Diminished elasticity of the lung tissue, as part of the elastic fibers, disappear and the number of surfactant-covered alveoli is reduced.
- An expiratory collapse of peripheral airways, trapping alveolar air in the periphery.

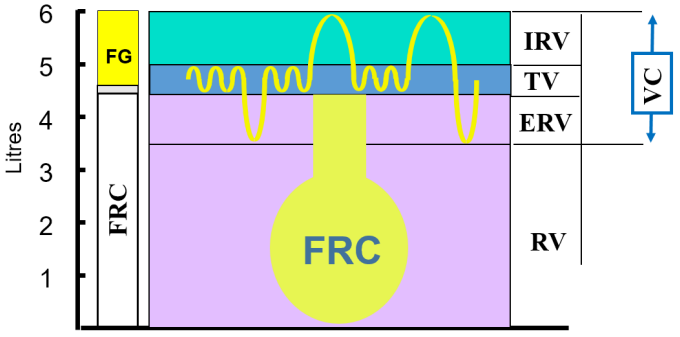

Figure 4-25. *Increased FRC reduces the vital capacity* (**VC**)*; tidal volumes may be maintained, but are small relative to the FRC. The ability to increase the volume of fresh gas* (**FG**) *relative to the FRC is reduced, compare with fig 4-6.*

The consequences of these changes are an increased FRC, a normal tidal volume gives a reduced percentage of fresh gas added to the FRC with each breath (fig. 4-25) and an increased P_aCO_2.

As both chronic bronchitis and emphysema are present in various proportions in advanced COPD, the patients usually exhibit both reduced P_aO_2 and increased P_aCO_2 (RF type 2, see above).

Bronchial asthma.

Asthma is a disorder in which chronic airway inflammation is one of the hallmarks. The nature of the inflammation is, however, different from that of COPD (258) and has less destructive consequences, even if anatomical changes like airway wall thickening, fibrosis, and increased mucus production are seen in the later stages of the disease. It is often present already in childhood; with adequate treatment, the consequences for gas exchange during the stable state of disease are small or not detectable at all.

In addition to low-grade inflammation, it is characterized by airway hyper-reactivity to inhaled irritants, allergens, and cold air as well as to ingested foodstuff and drugs (259, 260). The hyper-reactivity leads to episodic, reversible increases in airway resistance (asthma attacks, fig 4-26), characterized by

- Contraction of bronchial smooth muscle.
- Edema of the airway mucous membrane.
- Secretion of viscous mucus.

Acute asthma attacks.
The degree of airway obstruction during such attacks determines the reduction in ventilation volumes and thus the changes in P_aO_2 and P_aCO_2. In most patients, there is a significant reduction in P_aO_2 but the P_aCO_2 is normal or subnormal during the initial phase (261, 262, 263) due to hypoxemia-driven ventilation increase. The P_aO_2 reduction is mostly due to inhomogeneous ventilation with reduced V/Q ratios; increased effort of respiratory muscles may reduce the S_VO_2 and contribute to the hypoxemia. In severe attacks, mucus plugging of small airways may lead to the development of intrapulmonary shunts.

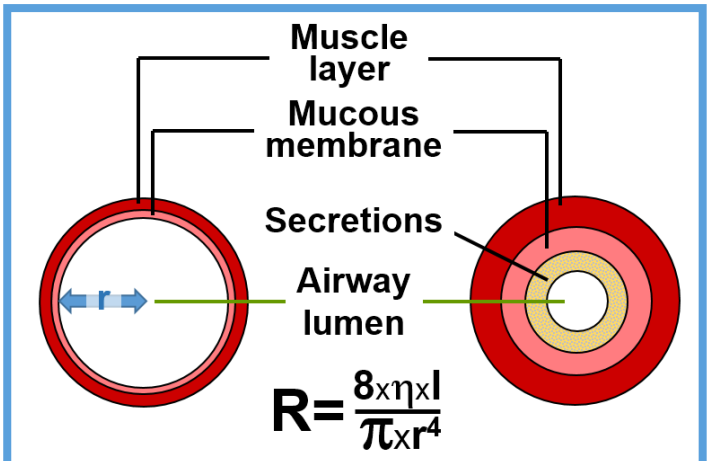

Figure 4-26. *Changes in airway resistance during asthma attacks. If the inner airway lumen is reduced to 1/2 of normal, the airway resistance increase 16 times (see Part 4-1, pg. 9).*

Increasing P_aCO_2 as a sign of respiratory muscle fatigue.
In severe asthma attacks, a rise in P_aCO_2 after an initial phase with normal or subnormal levels is an ominous sign, indicating that muscle fatigue and ventilatory decompensation has occurred. The need for mechanical ventilation support may then be imminent (264). In severe asthma, the O_2 consumption may be increased by as much as 60% (42), probably by a combination of stress (catecholamine effect on the metabolic rate) and the increased muscular effort. The increased $\dot{V}O_2$ may reduce the S_VO_2 and accentuate hypoxemia (see Part 4-2, shunt). The pressure between the pleurae blades (the intrapleural pressure) during spontaneous ventilation will be very low during the inspiration of even very small tidal volumes; during expiration, the pressures will be high. See Part 4-4 for support of ventilation during attacks.

Interstitial lung disease (ILD) and lung fibrosis.

The umbrella term ILD comprises a wide variety of inflammatory lung diseases (more than 300 (265)) where the inflammatory process, in opposition to that in COPD and asthma, is localized

primarily to the *interstitial* lung parenchyma. Varying degrees of interstitial fibrosis, reducing lung compliance, are found (266) and the alveolar air spaces may be involved. These diseases may be a result of

- **Exposure to external agents**, e.g. smoking, environmental and occupational agents, drugs, and radiation from radioactive agents.
- **Autoimmune or connective tissue diseases**, where lung dysfunction may be considered as a pulmonary manifestation of these diseases
- **Fibrotic process of unknown etiology**, e.g. Idiopathic pulmonary fibrosis (IPF).

The etiology of the disease is known in only about 35% of the patients (e.g. asbestosis, silicosis, and extrinsic allergic alveolitis); in the rest (e.g. sarcoidosis, idiopathic interstitial pneumonia, ILD as part of autoimmune disease), the etiology is unknown (265).

In most patients, shortness of breath during physical activity is the primary symptom; hypoxemia at rest is modest but increases during exercise while CO_2 excretion is maintained (267); hypercarbia is a late symptom. As fibrosis is part of the picture in many patients, the ability to increase tidal volumes in response to increased O_2 consumption is decreased (268). In patients with IPF, part of the reason for hypoxemia, especially during exercise and increases in $\dot{V}O_2$, may be due to diffusion limitation across the alveolar-capillary membrane. If the disease progresses to the point where ventilator assistance is needed, mortality is high (269). For more details about this group of diseases, see a review in ref. 270.

Cystic fibrosis.

The disease is characterized by bronchiectasis and bronchial obstruction and is a result of a genetic defect in the function of secretory cells in the mucous membranes of the body. Inactive or dysfunctional variants of a membrane protein, the cystic fibrosis transmembrane conductance regulator (CFTR), cause secretions to be thicker and more viscous than normal. In addition to obstruction of the airways, the secretory dysfunction of pancreatic and other intestinal secretions may cause gastrointestinal diseases (pancreas insufficiency and pancreatitis, meconium ileus, and biliary tract obstruction, see ref. 271).

The lungs are the organs most commonly affected. The thick secretions impair the airway mucociliary function and make secretions harder to eliminate, stagnant secretions cause bronchial obstruction and act as a reservoir for microorganisms. In the western world, *Pseudomonas aeruginosa* is the most common colonizing agent found in adolescents and adults (272).

The chronic presence of bacteria attracts and activates leukocytes, primarily neutrophil granulocytes, which damage the airway tissue through their release of reactive oxygen intermediates (ROI) and proteases (see also Part 2-4) and leads to scarring and deformation. Also, the pro-inflammatory system in CF patients may be primed to react stronger than usual (273).

Tuberculosis (TB).

Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*. The bacterium causes a slowly progressive destruction of many types of tissue (e.g. bones and joints, lymphatic tissue, pleura, and meninges (274)); its pulmonary manifestation is the most lethal. A vaccine against the disease was developed early during the first part of the 1900s (BCG vaccine, based on an attenuated strain of bovine tuberculosis); it offered some, but not universal, protection. After effective antibiotics were introduced in the 1940-60-ties, it was almost eradicated in the western world (275). It is still, however, an important cause of serious pulmonary disease in the developing world, and new strains, more resistant to antibiotics, are on the rise.

The spread of the human immunodeficiency virus (HIV) has also led to its resurgence, with an estimated 8.9 to 11 million new cases globally, and 1.1-1.3 million fatalities (276). A far greater number of patients are infected but have latent, incipient, or subclinical infections (277).

The inflammatory processes cause many of the same changes and symptoms, including night sweats, as those observed in patients with COPD from non-tuberculous infections. Many older patients with COPD have had TB previously. The process may consist of multiple foci (miliary or disseminated tuberculosis presenting as multiple infiltrates on a plain X-ray), or be dominated by a smaller number of tuberculous cavities, which may be envisioned as gigantic emphysematous caverns that can reach a diameter of 4 cm or more. If the tissue destruction also extends to branches of the pulmonary artery, hemoptysis occurs. The presence of hemoptysis and failure to respond to common broad-spectrum antibiotics should lead to suspicion of TB (278). A lesion causing rupture of a larger pulmonary artery may cause a major hemorrhage to the airways, where the patients literally "drown in their own blood". In older literature, patients with observed hemorrhages exceeding 600 ml over 16 hours were reported to have a 75% mortality (279). Patients with disseminated tuberculosis may in rare instances present with symptoms compatible with ARDS (280, 281); in which case the mortality is close to 90%.

4-4. RESPIRATORY FAILURE: TREATMENT OF HYPOXEMIA AND HYPERCARBIA, MONITORING

TREATMENT OF RESPIRATORY FAILURE - GENERAL PRINCIPLES

In the initial phase of severe hypoxemia, the focus should be on maintaining, or re-establishing, adequate oxygenation of the blood. Severe hypercapnia is, *per se*, much better tolerated than severe hypoxemia; even total apnea does not create a dangerous acidosis in resting persons before 20-30 minutes have elapsed. In hyperacute situations, the primary focus is therefore always on maintaining or re-establishing an acceptable P_AO_2 (and thus P_aO_2 and S_aO_2), while treating increases in CO_2 usually are of secondary importance. Severe respiratory acidosis may, however, reduce the S_aO_2, and thus the DO_2, when P_aO_2 is low (fig 4-12). Therapeutic interventions may roughly be grouped into

- **Supportive interventions.** These include *all types of interventions* whose primary goal is to maintain blood oxygenation *and* the delivery of adequate amounts of O_2 to the tissue. At the same time, dangerously high arterial CO_2 levels and severe respiratory acidosis must be avoided if possible. Supportive interventions have little, or no, beneficial effect on the underlying pathological processes *per se*; the use of unnecessary high F_iO_2 or ventilation volumes may aggravate the damage to the lungs, both should be individually calibrated.
- **Specific interventions** include all interventions that can ameliorate or eliminate the underlying cause of the failure. Successful interventions may re-establish normal (or at least adequate) gas exchange conditions within minutes to hours (see below). Examples of common specific interventions are the removal of mechanical airway obstruction/occlusion and drainage of large masses of air or fluid from the intrapleural space. In pneumonia, the administration of antimicrobiological agents is a specific intervention, but the effect usually takes days.

Supportive interventions are always indicated in emergencies until specific interventions, if indicated and available, can be carried out successfully.

GOALS FOR SUPPORTIVE THERAPY.

General treatment goals.

The primary goal of treatment in patients with hypoxemia and/or hypercarbia is *not* to re-establish *normal values* of PO_2, CO_2, and pH in arterial blood, but to secure that the combination of **Hb**, **S_aO_2** and **C.O.** result in an adequate O_2 delivery to the organism. Alleviating hypoxemia and avoiding life-threatening respiratory acidosis without damaging the lungs further are fundamental goals; the negatve effects of the chosen interventions (e.g. CPAP, IPPV, see below) on the circulation should also be as small as possible. The latter is especially important in emergencies with unstable circulation and when hypovolemia is suspected.

Priorities in emergencies.

In hyper-acute states with grave hypoxemia on the verge of becoming lethal (e.g. respiratory arrest, acute upper airway occlusion, failure to intubate/ ventilate after induction of anesthesia), securing adequate P_AO_2 (and hopefully also DO_2) by whatever means available takes priority over the risk of increasing PCO_2 and other potentially damaging aspects of treatment (see below). Even if severe respiratory acidosis depresses the ability of the heart to mount a compensatory response to a low C_aO_2 and induces a rightward shift of the HbO_2 dissociation curve with a reduced S_aO_2 when P_aO_2 is suboptimal, a rise in blood CO_2 represents only a modest danger compared to severe hypoxemia during the first minutes of grave respiratory insufficiency or -arrest.

Priorities after stabilization.

When control of the situation has been achieved (i.e. adequate DO_2 can be assumed or verified), but the condition of the patient and type of respiratory failure make prolonged manual or mechanical ventilator assistance likely, the focus shifts to

- **Avoidance of F_iO_2 levels and ventilation modes that may damage the lungs further** (see permissive hypoxemia and hypercarbia below).
- **Minimize possible negative effects of increased airway and intrathoracic pressure on the circulation.** In most patients, application of positive airway pressures reduces diastolic filling and may increase the pulmonary vascular resistance, both effects may depress the C.O. in most non-cardiac circulatory failure patients.

The level of DO_2 necessary to meet the O_2 requirements of all tissues varies with the type and stage of disease, as well as with ongoing treatments (e.g. catecholamine infusions) and body temperature. Suspicion of tissue hypoperfusion in localized areas (e.g. increased intracranial pressure, compartment syndromes) usually mandates a higher C_aO_2 and perfusion pressure. Which goals of DO_2 and PCO_2 to aim for after stabilization has been achieved should be continuously re-evaluated when the treatment effects on arterial and venous blood gases stabilize.

Permissive deviations in P_aO_2/S_aO_2 and P_aCO_2.

Permissive hypoxemia, the concept of accepting subnormal P_aO_2/S_aO_2 values to minimize ventilator-associated lung injury and thus avoid the potential toxic effect of increased F_iO_2 on the lungs, has been advocated by some authors (282). A target P_aO_2 allowing for moderate hypoxemia (P_aO_2 7.3-10.7 kPa (55-80 mmHg) *or* S_pO_2 88-95%) was used in the ARDS Network Trials (18, 283), others have defined permissive hypoxemia as a more extreme reduction of S_aO_2 to the 82-88% range (284). Targeting a lower P_aO_2 in ARDS patients (8 kPa (60 mmHg) vs 12 kPa (90 mmHg)) in a recent multi-center study did not, however, reduce mortality (285). In another study of ARDS patients, targeting a low P_aO_2 of 7.3-10.7 kPa (55-80 mmHg) vs a normal range of 12-14 kPa (90-105 mmHg) not only failed to reduce mortality in the lower target group but instead increased it; intestinal ischemia seemed to be a special problem in the permissive hypoxemia group (286). Thus, the negative effects of utilizing F_iO_2 levels that result in normal or slightly reduced P_aO_2/S_aO_2 seem to be of modest importance in most patients; also, levels of hypoxemia which is acceptable in some groups of individuals (i.e. those with an adequate circulatory reserve) may not be acceptable in others with co-morbidities that may, or may not, be known.

Focusing solely on the patient's S_aO_2/P_aO_2 levels in the blood without estimating the corresponding DO_2 is too simplistic. There is a large variation in circulatory co-morbidities in patients with lung failure; young trauma victims with posttraumatic ARDS in a surgical ICU can be expected to have circulatory reserves far above those found in the usually older patients in a medical ICU. The ability of each individual to mount an adequate circulatory response (Part 3-1) *and* the mass and functional state of their Hb are important factors for whether or not a targeted P_aO_2 and S_aO_2 results in a DO_2 that ensures aerobic metabolism in all perfused tissues. Treatment of circulatory failure (see Part 3-4) and, when indicated, erythrocyte transfusions may thus be a necessary part of the strategy to secure an adequate DO_2 in some patients with respiratory failure, as also argued in ref. 284.

Whether, when, and to what extent, permissive hypoxemia should be an accepted strategy in ARF must thus depend on an individual evaluation of each patient. Such evaluation is difficult in the initial stage of trauma and disease; in the author's opinion, permissive hypoxemia in ARF is

a concept to be considered only in previously healthy, circulatory stabilized patients in whom continuous monitoring of blood oxygenation and cardiovascular function has been established.

Permissive hypercarbia is the concept of accepting supernormal P_aCO_2 levels to minimize the risk of ventilator-associated lung injury in patients with severely diseased lungs. It allows the use of small tidal volumes, a strategy that is widely assumed to protect against ventilator-induced lung injury (186), and moderate increases in P_aCO_2 is generally well tolerated. Some studies have shown a beneficial effect of using a ventilation mode that allowed the P_aCO_2 to rise to mean levels of 8.7 kPa (65 mmHg) (287) or at least above 6 kPa (45 mmHg) (288). A protective effect of hypercarbia *per se* on the lungs has been proposed but has not been proven (289, 290).

Acute hypercarbia may, however, have several potential negative effects on the organism (291). Increased P_aCO_2 leads to respiratory acidosis with negative effects on circulation and a rightward shift of the HbO_2 curve; it also stimulates the respiratory apparatus and attempts at spontaneous ventilation, which may require increased sedation to avoid patient-ventilator asynchrony (291). The latter may be associated with increased mortality (292).

A retrospective study found hypercarbia during the first 38 hours in the ICU to be associated with increased mortality (293); the observed hypercarbia may, however, be a surrogate indicator of lungs that were difficult to ventilate and therefore represented patients with more severe respiratory failure. Case reports describing very high P_aCO_2 levels in patients indicate that such levels can be compatible with a good outcome as long as simultaneous hypoxia is avoided (see also pg 296). Thus, at least for a limited time, severe hypercarbia without hypoxemia may be well tolerated by most patients; and is preferable to the use of high tidal volumes and pressures in ARDS patients (see positive pressure ventilation below).

SUPPORTIVE INTERVENTIONS THAT MAY IMPROVE, OR ELIMINATE, HYPOXEMIA DUE TO LUNG FAILURE

Interventions and **choice of devices** should be adjusted to the severity of hypoxemia-hypercarbia, the presumed future development of the underlying condition should also be taken into consideration. An overview of interventions, in escalating order, is given below (see also fig. 4-27).

In patients with adequate spontaneous ventilation.

① **Increase the mean P_AO_2 by increasing the F_iO_2 –** i.e. administration of supplementary O_2. Medical grade compressed O_2 and devices for supplementing inspired air with extra O_2 are readily available to medical personnel in most settings. The effect on P_aO_2/S_aO_2 may be modest in patients where shunt is the predominant pathophysiological change (see below).

② **Increase the effective alveolar-capillary surface area** by increasing the airway pressures and avoiding atelectases using Continuous Positive Airway Pressure (**CPAP**), typically in the 5-10 cmH_2O range. This may also dilate small airways and reduce work of breathing, but *can* reduce C.O. Simple CPAP systems are easy to use and may be utilized also in pre-hospital settings.

Additional interventions in patients with inadequate ventilation.

③ **Secure adequate tidal volumes by assisting the patient's spontaneous breathing – "assisted ventilation".** Applying manual- or machine-assisted augmentation of airway pressures during inspiration while maintaining a positive end-expiratory airway pressure (**PEEP**) may, in addition, control the PCO_2. Equipment for non-invasive assisted or controlled ventilation (bag

and face mask) is available to medical and paramedical personnel in most settings. Manual ventilation *assistance* requires some experience, machines for *advanced* ventilation support are usually localized to intensive care units (ICU) and operating rooms.

④ **Secure adequate ventilation volumes by controlling tidal volumes and their frequency –"controlled ventilation".** Tidal volumes are secured by applying manual- or machine-controlled cyclic changes in airway pressures; the pressure increase (i.e. tidal volumes) and frequencies are determined by medical personnel, and a PEEP is maintained. Simple transport ventilators are often available for pre-hospital use in industrialized countries. Equipment for placement of endotracheal tubes or larynx masks are often available, but correct use requires experienced personnel.

⑤ **Anti-atelectasis measures.**

The "Open lung concept" aims at increasing the effective gas exchange areas by opening atelectatic alveolar areas and/or preventing further atelectasis. Several methods are utilized: Recruitment, Airway Pressure Release Ventilation (APRV), Prone positioning, High-Frequency Jet Ventilation (HFJV), and High-Frequency Oscillatory Ventilation (HFOV)), see below.

⑥ **Pharmacological interventions in ARDS and other states.**

Inhalation of Nitrogen monoxide, Prostacyclin, Surfactant, β_2-agonists, Corticosteroids, plus intravenous injections/infusions of Corticosteroids, β_2-agonists, etc.) may improve gas exchange.

⑦ **Employing devices for oxygenating the blood and/or removal of CO_2 <u>outside</u> the body.** These can be grouped into Extra-Corporeal Membrane Oxygenation (ECMO), Extra-Corporeal Lung Assist (ECLA), and Extra-Corporeal CO_2 Removal ($ECCO_2R$), see below. Devices for extracorporeal blood oxygenation require substantial resources and expertise, such treatment is usually available only in larger teaching hospitals and specialized institutions.

Even if blood oxygenation can be improved by the three latter types of interventions, the evidence for an impact of their routine application on mortality and morbidity is still not conclusive.

GENERAL INDICATIONS FOR INTERVENTIONS TO IMPROVE HYPOXEMIA/ HYPERCARBIA

Considering the large variations in pulmonary and extra-pulmonary conditions that may induce lung dysfunction and cause hypoxemia and hypercarbia, no single strategy can be expected to prove optimal for all patients with acute respiratory failure. Recommendations that will benefit the majority of patients are not necessarily optimal for all patients.

Also, different strategies and rules should apply when dealing with hyper-acute emergencies where the diagnosis is uncertain and resources are scarce, and when dealing with diagnosed conditions in a modern, well-equipped ICU.

All interventions may, at least theoretically, have negative aspects. A fear of negative consequences must not lead to avoidance of therapeutic action. Acceptance of the potential for harm must be reasonable relative to ***i)*** the *gravity* of the situation and ***ii)*** the assumed *consequences* of *<u>not</u> intervening*. Below are a few rule-of-thumb considerations that may be valid for the majority of patients with severe hypoxemia.

In Pre-hospital settings (i.e. no laboratory analysis or imaging available):

Awake, spontaneously breathing patients in acute clinical respiratory distress should always be given supplementary O_2, administered by whatever devices available that can be assumed to

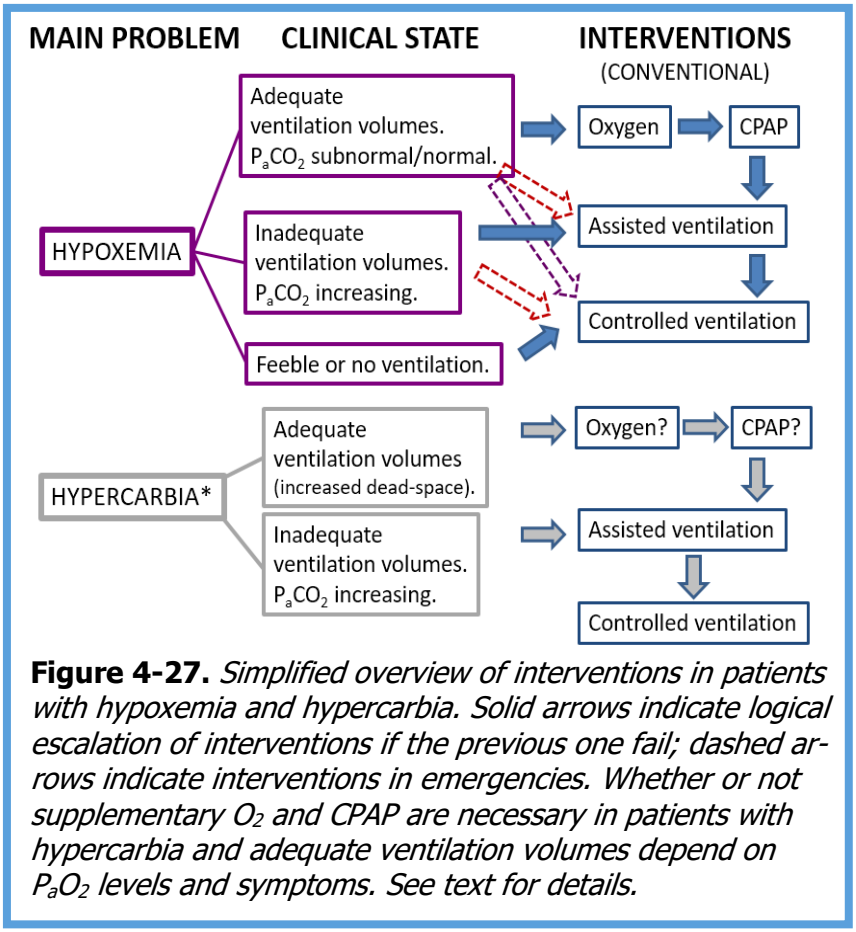

Figure 4-27. *Simplified overview of interventions in patients with hypoxemia and hypercarbia. Solid arrows indicate logical escalation of interventions if the previous one fail; dashed arrows indicate interventions in emergencies. Whether or not supplementary O_2 and CPAP are necessary in patients with hypercarbia and adequate ventilation volumes depend on P_aO_2 levels and symptoms. See text for details.*

deliver the highest possible F_iO_2 (see devices below). When reliable S_pO_2 (or blood gas) measurements become available, the supply of O_2 (i.e. the F_iO_2) can be titrated to obtain S_pO_2 values in the 92-95% range; higher levels may be desirable depending on the clinical presentation, tentative diagnosis, and the urgency of the situation.

In carbon monoxide intoxication (Part 2-3), in shock, and/or severe anemia, maximal O_2 delivery should be continued regardless of the result of S_pO_2 measurements (see Part 5-4) until reaching a facility with equipment for performing blood gas analysis that can discriminate between HbO_2 and HbCO.

Those with insufficient ventilation and/ or fulminant pulmonary edema should also receive CPAP or ventilation assistance by mask and bag, acute endotracheal intubation may be indicated in severe respiratory distress. Patients who in addition are unconscious should be intubated whenever possible to avoid aspiration of stomach contents, blood, secretions, etc. to the airways.

In-hospital settings (i.e. laboratory analysis, imaging etc. available):

- **P_aO_2 < 8 kPa (60 mmHg) despite F_iO_2 in the 0.40-0.50 range** in awake patients constitutes an indication for applying increased transpulmonary pressures (CPAP or NIV, see below), the choice of intervention depends on the tentative diagnosis and the patient's clinical state. Intubation should be considered if NIV does not stabilize the situation.
- **P_aCO_2 > 8 kPa (60 mmHg) in patients without previous chronic lung or respiratory muscle disease** *and* **acidosis** may be a signal of respiratory muscle fatigue; in severe asthma attacks, it should be interpreted as a danger signal as the need for urgent ventilation assistance may be imminent. In those where hypoxemia is abolished by supplemental O_2, a further rise in CO_2 may occur. This is *not* a contraindication to increasing the F_iO_2, but increased surveillance of breathing pattern and measurements of CO_2 levels are required.

Expected effect of increased F_IO_2 when intrapulmonary shunts are predominant.

Modest effects of increasing the inspired F_iO_2 can be expected if the hypoxemia is due *purely* to intrapulmonary or cardio-vascular shunts (see fig. 4-28 and 4-29 plus calculation examples in Part 4-2). *No positive effect* can be expected if the O_2-enriched gas fails to reach the alveolar areas due to *airway occlusion* or to *hypoventilation* to a degree where the inspired tidal volumes are *smaller* than the anatomical dead space.

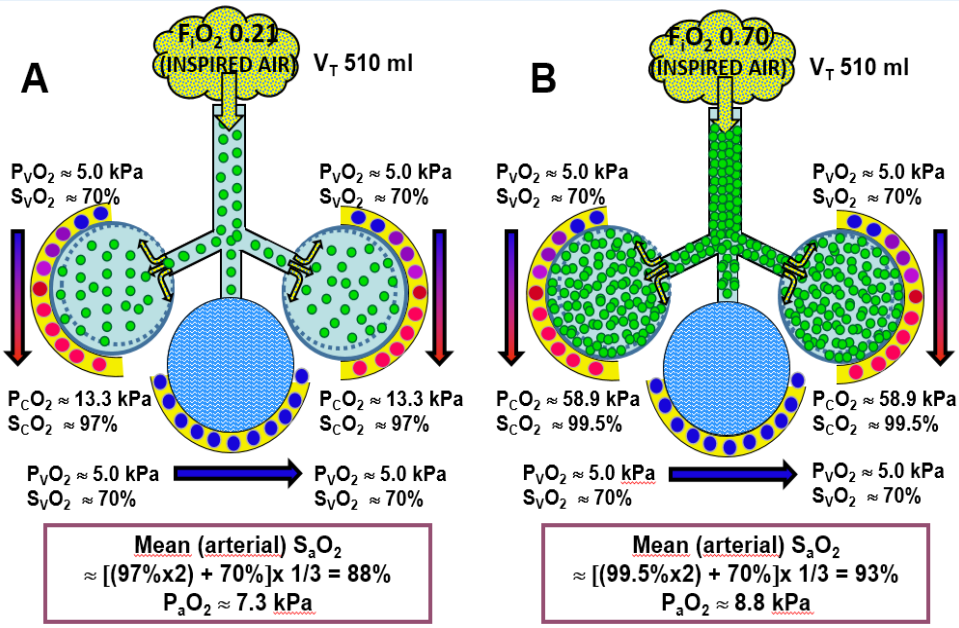

Figure 4-28. *Schematic drawing depicting the consequences of increasing the F_iO_2 for the arterial oxygenation if 1/3 of the total alveolar area are filled with edema fluid and the rest functions normally. The S_cO_2 of the blood draining the various alveolar compartment is calculated; the weighted mean SO_2 is close to the arterial value. For simplicity, the effect of the small increase in dissolved O_2 and a possible effect of alveolar hypoxia on perfusion (i.e. hypoxic vaso-constriction) is ignored.* **A***: Breathing room air.* **B***: Increasing the F_iO_2 to 0.70.*

If the shunt fraction amounts to 30% or more of the total pulmonary circulation in an individual with an Hb of 15 g/dl, a F_iO_2 of 1.0 (100% O_2) cannot normalize P_aO_2 and the O_2 content. If the pulmonary shunt fraction is around 50%, the increase in C_aO_2 from breathing room air to pure O_2 is in the 6-7% range (see fig. 4-28A). As most of the effect of an increase in P_AO_2 is due to an increase in dissolved O_2 in blood passing by ventilated alveoli, the effect of increased F_iO_2 on

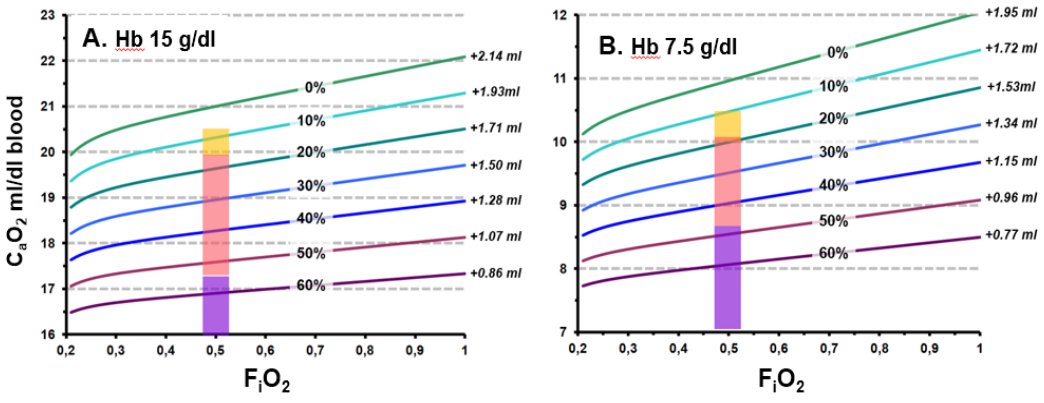

Figure 4-29. *Effect of increased F_iO_2 (x axis) on C_aO_2 (y axis) at various shunt fractions, assuming a constant C_VO_2.* **A***: Effect of increasing O_2 with an Hb of 15 g/dl, the increase in C_aO_2 (ml O_2/dl blood) at F_iO_2 1.0 compared to room air is shown to the right for the curves.* **B***: Smilar to A, but with Hb =7.5 g/dl. The C_aO_2 corresponding to P_aO_2/F_iO_2 levels defining ARDS at F_iO_2=0.5, is indicated for both Hb values: yellow=mild, light red=medium, violet=severe ARDS. Note the difference in magnitude of values on the y axis between A and B.*

C_aO_2 is close to independent of the Hb levels. The absolute C_aO_2 is, however, proportional to the Hb (compare fig. 4-29 A and B).

Other ways to increase P_aO_2 in patients with a large shunt fraction.

The O_2 content of the mixed venous blood is an important determinant for the PO_2 of the blood exiting the lungs with a substantial shunt (see calcualtions Part 4-2). As the S_VO_2 is a result of the ratio between the DO_2 and the $\dot{V}O_2$, increasing the former (by optimizing the C.O.) and/or reducing the latter (by reducing body temperature and the impact of other factors that increase the $\dot{V}O_2$) increases the O_2 content also of the arterial blood. The possible effect of increasing the S_VO_2 on the C_aO_2 in a patient with Hb=15 g/dl blood, relative to the effect of increasing the F_iO_2 as the sole intervention, is shown in fig. 4-30. A 15% increase in S_VO_2, used as an example in the figure, may be difficult to achieve in severely ill patients but even smaller increases may be important in grave hypoxemia.

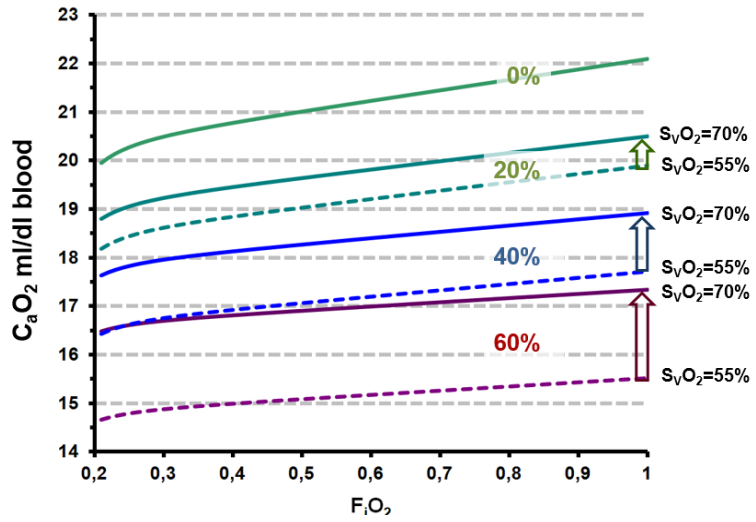

Figure 4-30. *Effect of increased S_VO_2 on the* **C_aO_2** *at 20%, 40% and 60% shunt and different levels of* **F_iO_2**. *Note that the lines for S_VO_2 55% and 70% are parallel, and that the effect increases with shunt percentage.*

Effect of increased F_iO_2 when low V/Q ratios represent the predominant derangement.

Contrary to the modest effect of increasing F_iO_2 when shunting is predominant, increased O_2 has a **substantial effect** if the hypoxemia is due to local, regional or global hypoventilation. Increasing the F_iO_2 may then *abolish the hypoxemia* altogether (see calculation examples in fig. 4-31). A device that supplies a F_iO_2 of 0.35-0.40 (35-40 % O_2) may double the alveolar O_2 concentration (i.e. the number of O_2 molecules) in hypoventilated alveoli and thus compensate for a 50% reduction in inspired fresh gas volume. A F_iO_2 of 1.0 increases the concentration of O_2 in alveolar gas to about 6.5 times normal after all the N_2 in the lungs and body fluid has been eliminated; this may take up to 5-10 minutes with normal tidal volumes.

Thus, a much smaller volume of inspired gas with increased F_iO_2 supplies even low V/Q alveolar areas with enough O_2 molecules to keep the alveolar PO_2 in the close-to-normal range. The P_aCO_2 in hypoventilated areas will, however, increase. If the tidal volumes stay normal, other alveolar areas receives a higher volume of fresh gas and excrete more CO_2. The degree of tidal volume changes determines whether ventilator support also becomes necessary (see below).

Relief of hypoxemia with increased F_iO_2 as a diagnostic tool.

The relative contribution of pulmonary shunts and regional hypoventilation to the development of hypoxemia is usually not known (except for in hydrostatic lung edema, aspiration of large amounts of fluid, total occlusion of a large airway *or* collapse of lung tissue, where shunt can be

assumed to represent the bulk of the pathophysiological changes). Supplementary O_2 should therefore always be administered to hypoxemic patients in clinical respiratory distress. The magnitude of the effect of supplemental O_2 on hypoxemia, i.e. the P_aO_2 increase in response to increased F_iO_2, represents a semi-quantitative indicator of the ratio between intrapulmonary shunt and low V/Q areas areas.

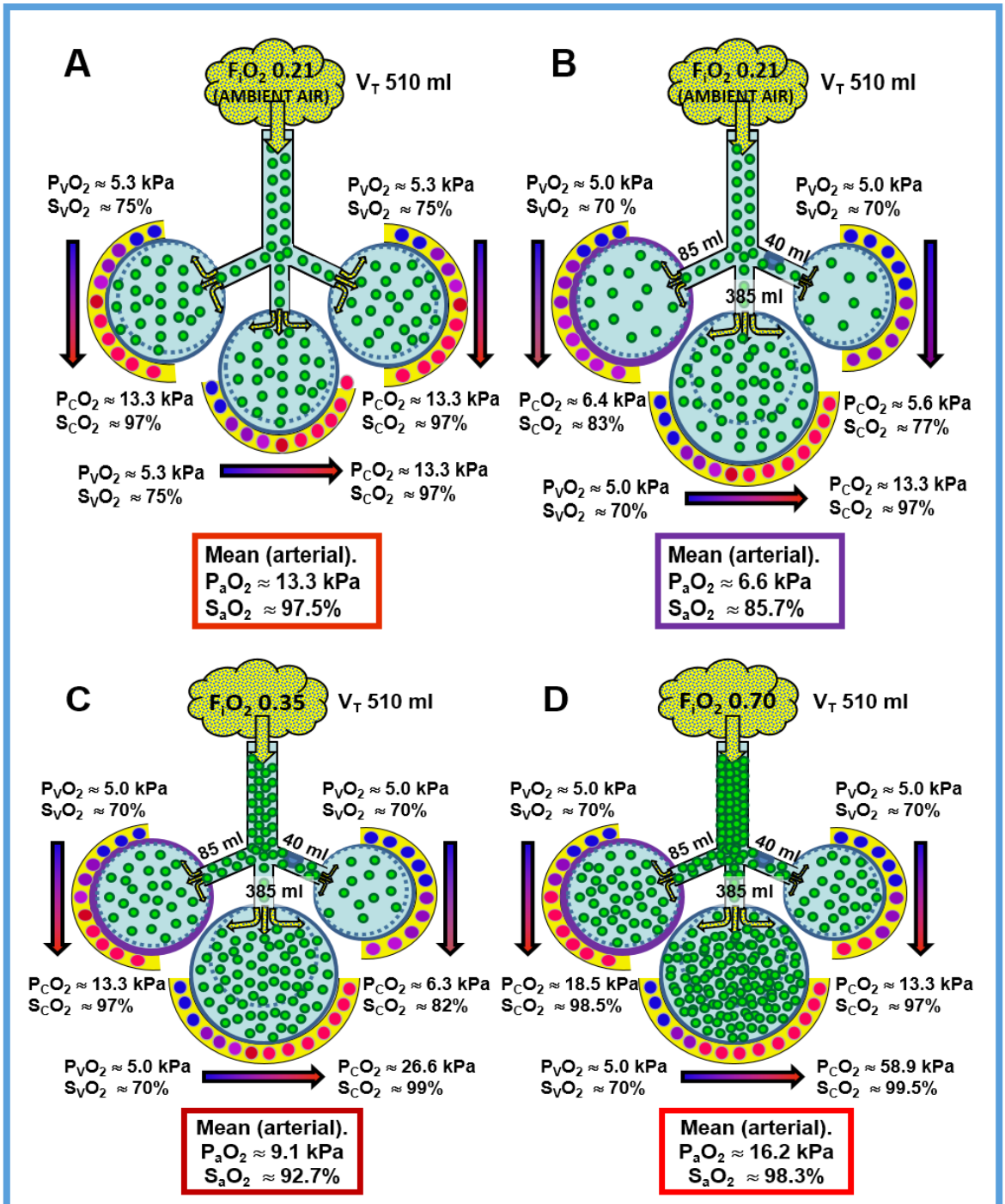

Figure 4-31. *Schematic drawing depiction of the consequences of regional changes in V/Q distribution, and the effect of increasing the F_iO_2 on oxygenation of pulmonary capillary blood perfusing the alveolar units (P_CO_2, S_CO_2). Each "alveolus" represent 1/3 of the total alveolar area; for simplicity, a possible effect of alveolar hypoxia on perfusion is ignored and the mean P_CO_2 and S_CO_2 values for the capillaries perfusing the various compartments becomes the arterial values.* **A***: Idealized state with V/Q ratio close to 1.* **B***: Regional hypoventilation due to compliance increase (left alveolus) and increased airway resistance (right alveolus), breathing room air.* **C** *and* **D***: Effect of F_iO_2 = 0.35 and= 0.70, respectively, under conditions as in* B.

DEVICES FOR DELIVERING SUPPLEMENTARY O_2

Devices for low-to-medium F_iO_2 increase.

Supplementary O_2 can be administered by a multitude of devices (fig. 4-32), ranging from simple ones requiring a source of O_2, a flowmeter, and a catheter, to more elaborate set-ups with air-O_2 mixers and efficient humidifying systems. From a technical standpoint, the devices may be categorized into four types:

- **Creation of a separate ambient reservoir within a confined space** around the head or the whole body, where supplementary O_2 is mixed with air (e.g. oxygen tents or canopies, incubators, hoods, etc.). The flow of supplementary O_2 can be titrated to obtain a target percentage of O_2 in the gas surrounding the head, as continuously monitored by a sensor. If the space, as well as the gas flow, is large enough to prevent outside air to enter the reservoir during maximal inspiration, this percentage also defines the inspired F_iO_2.

- **Low flow open devices without control of the actual F_iO_2** (nasal and tracheal catheters; open masks with a variable fit, see fig. 4-32), where supplementary O_2 at a fixed flow rate is added to the inspired air. Medical personnel sometimes make assumptions about the F_iO_2 resulting from the use of such devices, utilizing tables (294) where the O_2 flow rate is assumed to be proportional to the F_iO_2. Such tables represent data obtained by calculations or mean values from model experiments, or from investigations where patients or volunteers are examined under strictly controlled conditions (see ref. 295). The effect of such devices on the true F_iO_2 in an individual patient depends not only on the flow of O_2 or of the O_2% of a preset gas mixture, but also on ***i)*** the fit of the device, ***ii)*** the patient's anatomy (i.e. the reservoir function of nasal- and mouth cavities), ***iii)*** the ventilation pattern (the rate of gas flow during inhalation) and ***iv)*** whether mouth- and nasal breathing is predominant (296, 297, 298, 299).

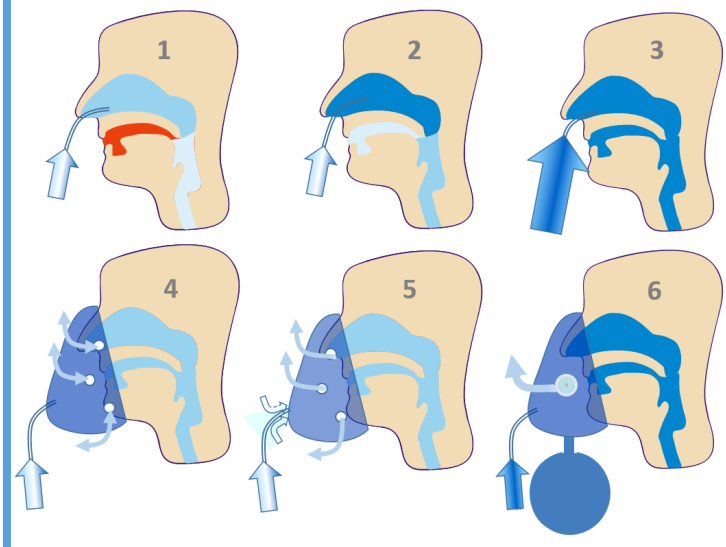

Figure 4-32. *Examples of devices for increasing the F_iO_2.* **1**. *Nasal catheter – low flow.* **2**. *Nasal catheter – medium flow.* **3**. *High-flow nasal catheter.* **4**. *Open facemask – medium flow.* **5**. *Open facemask with venturi valve.* **6**. *Tight-fitting mask with reservoir. In 1, 2 and 4, variations in patient anatomy and breathing pattern make assumptions about the amount of O_2 in the inspired gas (the F_iO_2) uncertain (see text).*

A maximum inspiratory effort in healthy adults may result in peak inspiratory flows of 200-400 l/min (300, 301); in most patients with various degrees of respiratory failure, it can be expected to be in the 15-70 l/min range (302, 303). Common to such devices is therefore that the amount of O_2 that mixes with the ambient air during inspiration, and thus the true F_iO_2, can vary widely (see below) from patient to patient. Examples of such devices are simple nasal catheters and –prongs, tracheostomy catheters, and bulbs, nasal masks, open face masks of various shapes *without* a reservoir space, etc.

- **Venturi principle face masks with F_iO_2 control**, where a jet of O_2 mixes with ambient air and the

flow and the dimensions of the jet nipple determine the fraction of O_2 in the gas inside the mask; various commercial nipple types are designed to give gas mixtures between 24% and 60% O_2. Whether this mixture also represents the true inspired F_iO_2 depends on the construction of the mask, the fit to the face of the patient, and the total gas flow.

Devices for medium-to-high F_iO_2 increase.

- **Low to intermediate flow devices with reservoirs.**

Such devices, with one-way valves and reservoirs, require tight-fitting masks and straps (or connection to tracheal cannulas, pharyngeal masks, and endotracheal tubes). As long as the flow is adjusted so that the reservoir does not collapse during maximal inspiration flow, the F_iO_2 is the same as that in the supplied gas flow. The gas supplying such devices usually comes from a gas mixer where the O_2 % (and thus the F_iO_2) can be set with reasonable accuracy.

- **High-flow nasal cannulas**,

When the flow of a gas with a pre-set O_2 fraction is high enough (typically 45-60 l/min) to avoid ambient air entering the upper airways during inspiration, the F_iO_2 is the same as that in the high-flow gas. Such high flow also increases the mean airway pressure and may augment the area of gas exchange through a CPAP effect (304)(see below). When using such flows, the gas must be fully humidified to avoid drying out and damaging the mucous membranes.

- **High-flow or gas reservoir devices connected to endotracheal tubes or tracheal cannulas**

When sealed with a cuff in the trachea, these devices deliver a pre-determined F_iO_2 from a gas mixer; their use requires a high-flow system or a reservoir combined with a one-way or a two-way valve (see CPAP systems below).

Devices for increasing the surface area available for gas exchange.

Positive end-expiratory pressure (PEEP) and Continuous positive airway pressure (CPAP). In the majority of patients with acute respiratory failure (e.g. hydrostatic pulmonary edema, ARDS), interstitial and alveolar edema increase the weight of the pulmonary tissue and extend the area of compression of both alveoli and peripheral airways in the most dependent part of the lungs.

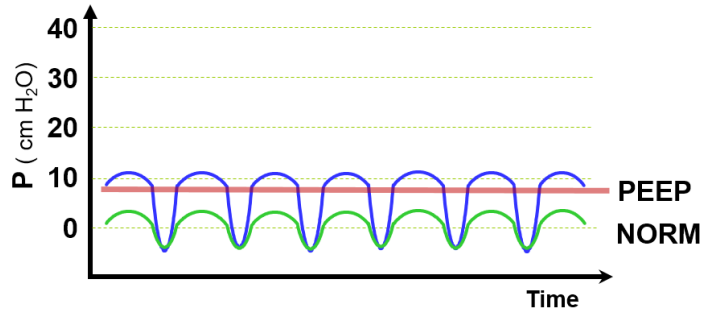

Figure 4-33. *Effect of applying a PEEP valve set to 10 cmH_2O to the expiratory flow during spontaneous ventilation (Blue curve) vs no PEEP (Green).To generate an inspiratory flow, the airway pressure must first fall from 10 cmH_2O to sub atmospheric. Pressures measured at lip level.*

Any device that increases the mean transmural airway pressure above normal at end-expiration (Positive End Expiratory Pressure - PEEP), when the gas volume in the alveoli is lowest, will counteract a collapse of alveoli and increase the number of functional alveoli-capillary units. Increasing the mean volume of acini and their alveoli also increases the alveolar surface available for gas exchange even if part of the acini are filled with alveolar edema.

After the observations of the beneficial effects of adding PEEP to mechanical ventilation in patients with ARDS, first published by Ashbaugh et al (173), the use of PEEP has become an integrated part of all treatment of acute respiratory failure, and also during positive pressure ventilation in general. Modern self-expanding bags for manual ventilation can usually also be fitted with a PEEP valve. During the application of increased levels of PEEP as the only intervention in spontaneously breathing patients, however, there is no increase in lung volume during the initial inspiration phase (fig. 4-33), which feels uncomfortable for many patients.

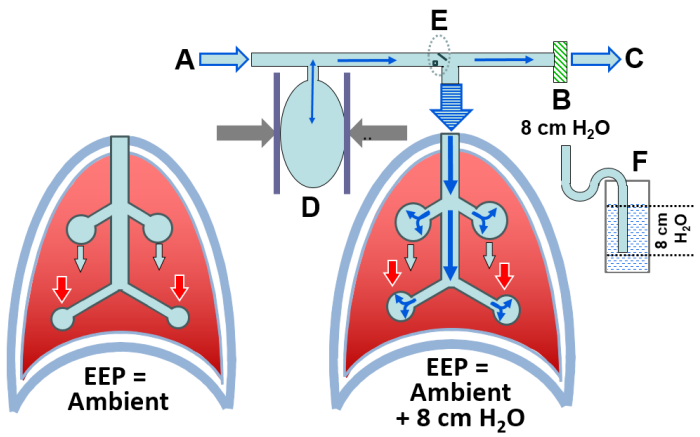

Figure 4-34. *Principle of an improvised circuit for CPAP breathing. Inflow of gas at* **A**, *before it exits, a PEEP valve* (**C**) *or a bubble seal* (**B**) *maintains a positive pressure in the system before the gas leaves the system. A pressurized reservoar* (**D**) *prevents loss of positive pressure during inspiration, a one-way valve* (**E**) *prevents expired air to enter the inspiratory limb of the circuit.* (**F**) *= adjustable water seal.*

Today, the most common way to increase the alveolar surface available for gas exchange during spontaneous ventilation is to increase the airway pressure above the ambient (typically 5-10 cmH_2O, higher pressure levels are also utilized) during the whole respiratory cycle. This principle (Continuous Pulmonary Airway Pressure – CPAP) is illustrated in fig. 4-34, see fig. 4-35 for the resulting airway pressures. If the pressure increase converts some of the shunt areas (atelectasis or partly fluid-filled alveoli) into low V/Q areas, or even to areas with normal V/Q ratios, the positive effect on P_aO_2 by even a modest increase in F_iO_2 may be substantial. This type of intervention improves or eliminates hypoxemia in many patients; in patients where localized hypoventilation is the major cause of hypoxemia, the effect of CPAP is more variable and high CPAP levels may have negative effects (e.g. alveolar hyperinflation).

Increased airway pressures may also reduce the resistance in the peripheral airways and, in some patient groups, a tendency to obstruction also of the upper airways during sleep or sedation may also be reduced (305). Even if devices creating a CPAP do not *per se* assist the ventilation, these effects may reduce the workload of the respiratory muscles and enable an increase in tidal volumes.

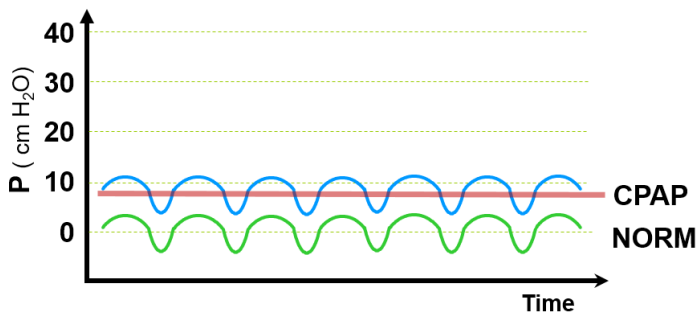

Figure 4-35. *Airway pressures during spontaneous breathing with a CPAP system (compare with fig 4-33 above), airway pressures stay above zero during the whole respiratory cycle.*

Many types of commercial CPAP devices are available – common to all, except for those employing very high gas flows, is that a tight seal with the airways is required. In addition, the gas flow must be high enough, or a pressurized reservoir large enough, to avoid a fall in pressure during peak inspiratory flow. High-flow cannulas (see above) can also create a

CPAP effect even without a tight seal, the magnitude of this effect is limited and cannot easily be titrated.

Under austere conditions, a CPAP system can be improvised utilizing a large (anesthesia) rubber bag, some pieces of tubing and a PEEP valve (preferably), or a water bottle (the bubbles make a lot of noise, and the vibration may damage the inner ear), following the principles depicted schematically in fig. 4-34.

Strategies for securing adequate tidal- and minute volumes.

Increasing the F_iO_2 or increasing the area of gas exchange have little effect on the P_AO_2 if the tidal volumes are so small of the inspired gas ventilates only the anatomical dead space and fails to reach the alveoli. A patent airway and tidal volumes of a magnitude that surpasses the volume of the anatomical dead space by a good margin are thus prerequisites for the two previous interventions above to benefit the patient. To secure tidal volumes of a necessary magnitude, patients may need ventilation assistance (i.e. spontaneous ventilation with an intermittent increase in the pressure of the inspired gas during inspiration) or, if the spontaneous ventilation is insufficient or absent, controlled positive pressure ventilation (see below).

General indications for manual or mechanical ventilation assistance *or* control in respiratory failure.

A. In patients where previously normal pulmonary function can be assumed:

- P_aO_2 < 8 kPa (60 mmHg) *despite* a F_iO_2 of at least 0.5 *and* CPAP of 5-10 cmH_2O.
- P_aCO_2 > 6-7 kPa (45-52 mmHg) *despite* hypoxemia.
- Respiratory rate > 35/min and increasing.
- Shortness of breath, cannot answer in whole sentences without breathing several times, or becoming more and more remote (cerebral hypoxia, general exhaustion).
- Reduced ability to cough, stagnation of secretions despite physiotherapy, adequate pain control, and stimulation.
- Increasing respiratory (or combined respiratory and metabolic) acidosis.

B. In patients with known chronic pulmonary conditions:

- P_aO_2 < 6-7 kPa (45-52 mmHg) despite F_iO_2 of at least 0.5 and moderate CPAP.
- P_aCO_2 > 8-10 kPa (60-75 mmHg), or considerably higher than the patient's normal value *despite* hypoxemia.
- Respiratory rate > 35/min and increasing. **NB**: falling respiratory rate and increasing remoteness may be seen when P_aCO_2 > 11-14 kPa ("carbon dioxide narcosis").
- Increasing acidosis, i.e. the patient's hypercarbia is no longer compensated for by an increased buffer base, often termed a *compensatory metabolic alkalosis* (see Part 5-3).

The rapid disappearance of an increased buffer base is usually accompanied by the development of lactacidosis, which in respiratory failure should be considered a grave warning sign. Other clinical guidelines are as above.

The blood gas levels indicated in A and B above assumes that P_aO_2 pressures are measured in patients at normal sea level and that the relation between P_aO_2 and S_aO_2 do not show extreme deviations from the standard HbO_2 curve. They do not *alone* constitute an absolute indication for ventilation assistance, especially if drug-related respiratory depression can be reversed by antidotes. Some patients may be candidates for ventilation assistance or support even if their blood

gas levels are better than those shown above, and *vice versa.* The combination of *several factors, including the clinical assessment by experienced doctors and nurses, should form the basis of the decision.*

A separate indication for positive pressure ventilation is to secure adequate oxygenation and CO_2 control in patients where injury or dysfunction of other organs require deep sedation, and where the degree of sedation usually leads to hypoventilation and hypoxemia. Traumatic and hypoxic brain injury has traditionally been the most common such indication; the now common induced hypothermia after cardiac arrest (see Part 3-3) represents another important indication for controlled mechanical ventilation of patients where the lung function *per se* may be normal.

Methods and devices for securing adequate ventilation volumes.

An overview of methods and devices for securing adequate ventilation is presented below. Interventions aimed at establishing a patent airway under various circumstances (body positioning, naso- or oropharyngeal tubes, endotracheal tubes, crichothyroidotomies, tracheostomies) are outside the scope of this compendium but are well described in various textbooks of Anesthesia and Emergency Medicine.

In some spontaneously breathing patients with patent airways, the capacity for generating adequate ventilation volumes may be seriously reduced (e.g. airway obstruction, respiratory muscle weakness or fatigue, internal or external restriction of inspiration). Such persons may need *ventilation assistance* to secure tidal volumes of a magnitude that ensures adequate addition of fresh O_2 to the alveolar gas space, as well as to eliminate sufficient CO_2 from it.

Assistance of the patient's spontaneous ventilation can be accomplished by

- Supporting the patient's inspiration by increasing the trans-pulmonary pressures (usually as Automated Pressure or Volume Support Ventilation – PSV or VSV – see below) during inspiration, increasing the airway pressure support until the tidal volumes become adequate.
- Allowing reduced spontaneous tidal volumes, but adding an extra "ventilation effect" on the alveolar gas by a cyclic change between two CPAP levels (Bi-Level or BiPAP ventilation, Airway Pressure Release Ventilation – APRV – see below) to control P_aCO_2, *or*
- Any combination of the above methods.

The magnitude of targeted ventilation volumes will vary between individual patients (see below), normal tidal volumes are not necessarily a goal in all patients and may in some situations (e.g. severe asthma attacks, mechanical airway obstruction) be impossible to achieve. Attempting to normalize ventilation volumes may injure the lungs in patients with substantially reduced FRC (see Part 4-3 VILI). Removal of CO_2 also suffers during hypoventilation, but may not be a critical factor as long as the PO_2 is maintained at acceptable levels. When hypoxemia is avoided by maintaining a high F_iO_2, increases in P_aCO_2 to about six times (306), seven times (307), and even more than nine times normal (to 49.7 kPa, 373 mmHg) (308) have been reported to be compatible with full recovery.

In non-breathing or poorly ventilating patients, adequate tidal and minute volumes can be achieved utilizing *controlled* manual- or mechanical ventilation. The creation of a pressure gradient between the alveoli and the upper airways may then be accomplished by *either* intermittently creating a negative pressure outside the thoracic cage (*negative pressure ventilation*, a principle mostly of historic interest, see below), *or* applying a positive pressure inside the airways (*Intermittent Positive Pressure Ventilation* - IPPV). When such methods fail to control

arterial oxygenation and/or CO_2 removal from the blood, extracorporeal methods (see below) may be an option for a limited number of patients.

Mechanical ventilation: two very different principles.

Negative pressure ventilation occurs when a sub-atmospheric pressure applied intermittently outside of the thoracic cage and abdomen induce a more negative transpulmonary pressure, while the ambient pressure around mouth and nose remains normal. The reduced extrathoracic and extraabdominal pressures cause expansion of the thoracic cage and a caudal shift of the diaphragm, which creates a negative pressure in the alveoli similar to that created by the inspiratory muscles during spontaneous ventilation. Ambient gas then flows into the alveoli along the pressure gradient.

This approach is the most physiological way to establish artificial ventilation and was tried out in many variations during the 18th and 19th century (171, 309). The first such device that gained general approval for clinical use and became common in specialized units was constructed as late as 1929; this and similar devices ("iron lung", "tank ventilator") were widely used for respiratory support in patients suffering from acute paresis of respiratory muscles due to poliomyelitis and similar conditions up to the 1960-ties. A negative pressure of 30 to 40 cmH_2O below atmospheric inside the tank during inspiration was needed to ensure adequate tidal volumes in most patients. The magnitude of the negative pressure that could be applied rapidly inside a tank ventilator was limited by both technical issues and the creation of tissue edema due to increased transcapillary hydrostatic pressures.

The most important drawback of the method was that diseased lungs with low compliance, high airway resistance, or both, did not expand properly. In addition, access to the patient's body was difficult and made care of the patient cumbersome; the airways were not protected against aspiration of secretions, bleeding, or abdominal contents. An alternative technique, the cuirass ventilator apparatus, which covered only the thorax and abdomen, made it easier to care for the patients and had its proponents. This method was also limited to use in patients with relatively normal lung/chest wall compliance and airway resistance. Today, the principle of negative pressure ventilation has mostly historical interest.

Positive pressure ventilation expands the alveoli when airway pressures rise relative to the ambient pressure. A compression (by manual or mechanical means) of a reservoir with inspired gas *or* an intermittent opening of a valve connected to a pressurized gas delivery system, increases the airway pressure and insufflates the lungs. When the period of supplying pressurized gas terminates and an outflow valve open, expiration occurs as a passive process.

The expansion of the airways by positive pressure changes, however, the distribution of the inspired gas within the lungs (fig. 4-36 and fig. 4-37). The insufflated air flows preferentially into alveolar areas of least resistance to expansion. In contrast to the situation during spontaneous inspiration, where most of the ventilation goes to the best-perfused areas, the nondependent part of the lungs receives most of the insufflated gas while the dependent part is best perfused. The consequence is that the V/Q ratio in the upper part of the lungs increases while that in the lower part of the lungs decreases. The V/Q distribution thus becomes more heterogeneous, and the gas exchange efficiency of the lungs is reduced.

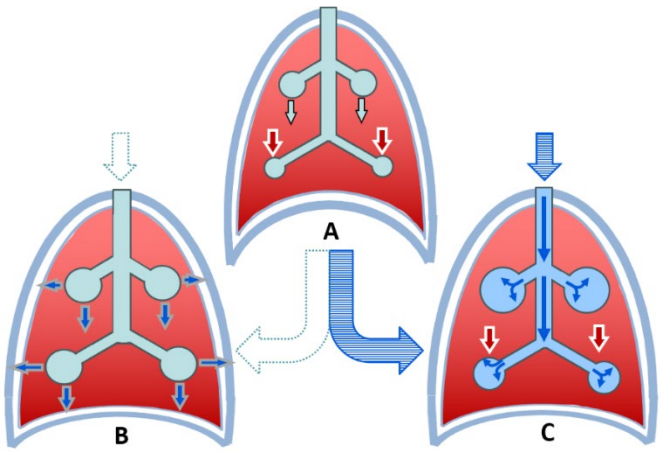

Figure 4-36. *Difference in distribution of inspired gas during spontaneous inspiration (***A** to **B***) and positive pressure insufflation (***A** to **C***) in the upright position. The insufflated gas follows the pathway of least resistance, which reduce the efficiency of gas exchange (see also Part 4-1).*

As the upper part of the lungs of a supine person receives most of the ventilation while the weight of the lungs and pressure of organs within the abdominal cavity impedes expansion of the dorsal-caudal part of the lungs, positive pressure ventilation used in the controlled mode may induce atelectasis also in persons with healthy lungs (see review in ref. 310). If the position of the body does not change intermittently, atelectasis will develop first in these areas. The atelectasis tendency is enhanced by obesity and increased edema of the pulmonary tissue.

Methods for applying positive pressure ventilation.

Isolated incidents of ventilation of the lungs by applying intermittent positive pressure to the upper airways by bellows or other devices have been tried on animals and lifeless humans for several hundred years; anecdotal descriptions of what could have been mouth-to-mouth breathing stretches back to the middle ages and even biblical times (311, 312). Various apparatus for non-invasive or invasive positive pressure ventilation through tight-fitting face masks or endotracheal tubes of various types (313), by manual or mechanical means, were constructed during the 1780 – 1910 period. Machines intended for long-term ventilation of intubated patients became available during the 1940-1950 period. Based on experiences from the life-saving use of manual positive pressure ventilation during the massive polio epidemic in Copenhagen in 1952 (where the primary problem was hypoventilation caused by respiratory

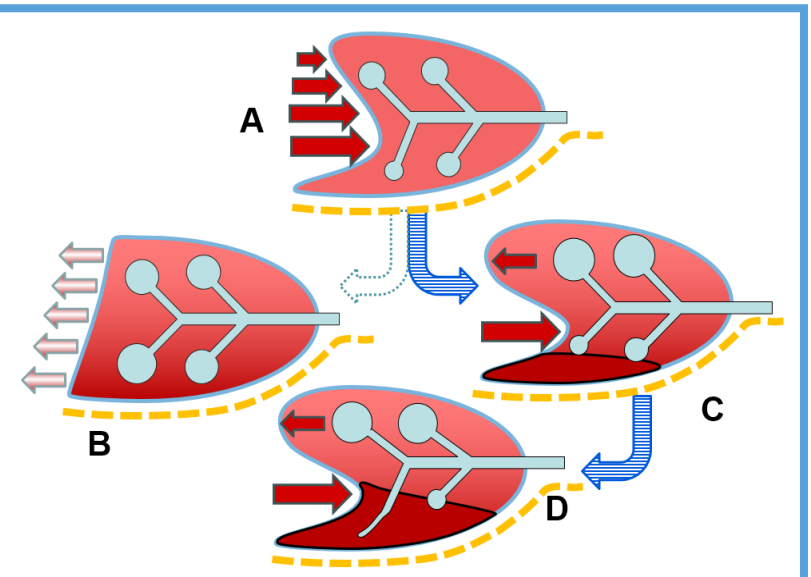

Figure 4-37. *Distribution of inspired gas in the supine position during spontaneous* (**A** to **B**) *and positive pressure* (**A** to **C**) *ventilation. At end expiration* (**A**), *with a relaxed diaphragm, the abdominal contents force the diaphragm upwards. During contraction* (**B**), *the volume of the cranial-dorsal lung area increase most and thus receive most of the inspired air. During insufflation with a relaxed diaphragm* (**C**), *the compliance is highest where the pressure from the abdominal contents is smallest, i.e. the non-dependent part. The cranial-dorsal part, which receives most of the perfusion, is hypoventilated* (low V/Q ratio). *Hypoventilation may cause atelectasis and create shunt areas* (**D**).

muscle paresis, with secondary atelectasis), positive pressure ventilators came into general use in all sorts of patients with acute respiratory failure. The care of such patients was in many hospitals concentrated to specialized wards (Respiratory care units), which evolved into today's intensive care units (ICUs).

The first mass-produced machines for positive pressure ventilation were strictly volume-controlled (i.e. a given flow for a set period defined the tidal volume, see below); they were in many ways just a somewhat more controlled, and less manpower-intensive, replacement of manual ventilation with a bag. The resulting pressures in the upper airways were a function of ***i)*** the set volume and insufflation time, ***ii)*** the compliance of the lungs, and ***iii)*** the airway resistance. Next came simple pressure-controlled ventilating machines, where inspiratory flow ceased when a pre-set airway pressure was reached. More advanced pressure-controlled ventilators followed, in which peak airway pressures and inspiration time were set; the lung compliance and airway resistance determined the tidal volumes. The ability of the patient's inspiration efforts to trigger delivery of a pre-set gas volume was also introduced; this facilitated synchronization between the patient's inspiratory efforts and the inspiration phase of the ventilator.

Today, ventilation assistance to persons with acute respiratory failure focuses on *controlling the tidal volumes* and *optimizing the surface areas of gas-filled alveoli* (i.e. the total alveolar-capillary space). The former is accomplished by intermittently applying positive pressure to the airways by manual or mechanical means during inspiration, the latter by keeping the end-expiratory pressure (PEEP) above the ambient pressure during expiration and until the next inspiration.

In those with some degree of spontaneous respiration efforts, adequate tidal volumes may be attained by sensing the start of inspiration and then assisting the patient's breaths by adding extra pressure to the airways (i.e. increasing the transpulmonary pressure) during the whole inspiratory phase. The *primary goal* is such treatment is to ensure an adequate O_2 supply to the alveolar gas and keep the alveoli open, the *secondary goal* is to control the P_aCO_2 levels. A *bonus effect* is a reduction of the work of the respiratory muscles, and thus the O_2 consumption (see $\dot{V}O_2$ effects on S_vO_2 and P_aO_2/S_aO_2 above).

A multitude of equipment, techniques, and ventilator modes are available today, a detailed discussion of all of them, as well as the merits of the different modes, are outside the scope of this compendium. A short overview of some of the basic principles and concepts for assisting and controlling ventilation is, however, presented below.

VENTILATION MODES AND VENTILATOR SETTINGS

Invasive ventilation.

Invasive ventilation is positive pressure ventilation where the gas enters the upper airways through endotracheal tubes or tracheostomies, bypassing the nasopharynx and reducing the volume of the anatomical dead space. For decades after mechanical positive pressure ventilation became common therapy in respiratory failure, this was by far the most common method. In the acute phase, an oral or nasal endotracheal tube was utilized; if prolonged mechanical ventilation was necessary, a tracheostomy was often performed after 10-14 days. Whether this practice is beneficial for the outcome in patients with acute respiratory failure is still a topic for discussion; one retrospective analysis of endotracheal tubes vs tracheostomies indicated a better outcome for tracheostomized patients (314), but neither a meta-analysis (315) nor a prospective study (316) could confirm this. Tracheostomy is, however, better tolerated in awake or lightly sedated patients, and shortens the time on a ventilator (see also weaning).

Before elective endotracheal intubation, all patients should, if possible, receive supplementary O_2 (preoxygenation) and be connected to a pulse oximeter, continuous ECG, and a device for automated blood pressure measurement (invasive or non-invasive). After introduction of the tube, movement of the thoracic wall should be inspected and the respiratory sounds checked over both lungs. In patients with pronounced em-physema and a markedly barrel-shaped thorax, it may be difficult to see a movement of the thoracic wall; the respiratory sounds may be diffuse and remote. In such patients it is of particular importance to observe the S_pO_2 closely, and if possible measure the end-expiratory CO_2 with a capnograph (if the tube is lodged in the esophagus, the CO_2 content of expired air rapidly approaches zero).

Incorrect intubation, wrong tube position, or a fault in the respirator/tubing circuit that prevents effective ventilation will normally produce an acute fall in oxygen saturation in patients with pulmonary failure within 20-90 seconds, depending on the effectiveness of preoxygenation. However, fully preoxygenated patients *without* pulmonary failure can maintain a normal S_aO_2 even after 2-3 minutes of apnea (see Part 4-1). Controlling the tube position by X-ray after emergency intubations should be done as quickly as possible, preferably within 1-2 hours after intubation. In patients with a high P_aCO_2, it is important not to lower the CO_2 level too rapidly, but to allow reduction to the desired level to take place over many hours. Rapid reduction may lead to a severe decrease in blood pressure and unintended alkalosis.

Non-invasive ventilation.

Non-invasive ventilation is a method where positive pressure is applied through a mask that creates an air-tight seal, avoiding both the trauma and anesthetic drugs involved in the intubation procedure and the discomfort in the larynx. The use of masks in this setting does not protect against aspiration or some of the pressurized air entering the esophagus during inspiration; also, there are difficulties involved in keeping a patent seal when airway pressures are high. Non-invasive ventilation is, therefore, best suited for patients with moderate respiratory failure, especially those with COPD exacerbations and cardiogenic pulmonary edema; also if the duration of ventilator assistance is assumed to be short (317, 318). Non-invasive ventilation support can be considered as a mode *between* mask CPAP and invasive ventilation; although less traumatic than invasive ventilation, it is not without complications.

Laryngeal mask airway.

Laryngeal masks have become increasingly popular as an airway during anesthesia, and are to some extent also used in prehospital settings; they may also be useful in situations where neither intubation attempts nor mask ventilation proves successful. It is more invasive than masks and catheters, but less so than an endotracheal tube. The "invasive" part consists of a mask-like device to be placed in the hypopharynx; it offers some degree of protection against aspiration but not on the same level as a cuffed endotracheal tube. It is not suitable for long-term ventilation, nor in awake or only lightly sedated patients (reviewed in refs 319, 320).

To intubate – or not – in acute respiratory failure.

Unconscious patients, patients who need to be heavily sedated, or suffer from paresis of pharyngeal muscles, are not protected against aspiration of secretions or stomach contents during NIV. Also, the peak pressures that can be employed are more limited. In most patients with acute and severe respiratory failure, who are already in clinical distress, invasive ventilation is still the most reliable option in the acute phase. Primary acute tracheostomy is generally only carried out in patients where upper airway obstruction represents a major part of the problem, or where abnormal anatomical conditions prevent the placement of endotracheal tubes using normal techniques.

The technical aspects of the endotracheal intubation procedure require skilled medical- or paramedical personnel. The often accompanying sedation of awake patients also carries a risk of circulatory instability. Patients who have been in progressive respiratory failure for some time may be dehydrated and hypovolemic, intermittent positive pressure ventilation in such patients often reduces diastolic filling of the ventricles and impedes cardiac function. Drugs given to facilitate intubation may also have a cardiodepressant effect. In addition, the patient's sympathetic tone, which often is elevated because of stress, hypoxemia, and acidosis, become reduced when sedative and other drugs are given in connection with intubation. The combination of reduced C.O. *and* systemic vascular resistance may sometimes result in severe reductions in arterial blood pressure and thus also in coronary perfusion pressure. Clinically dehydrated patients should, if possible, be given 0.5-1 liter of i.v. fluid before intubation and the start of positive pressure ventilation. Tidal volumes and PEEP should be started at modest levels until the circulation is stabilized. In acute pulmonary edema due to LV failure, such circulatory consequences are less probable but care should nevertheless be exercised. The combination of severe acidosis and hypoxemia increases the risk of arrhythmias in connection with intubation. For this reason, it is important to improve oxygenation (if possible) by inhalation of 100% oxygen (using a mask with a tight seal) before intubation.

Whether or not to try NIV as an alternative to invasive ventilation initially depends on the severity of the respiratory failure, the presence of co-morbidities, the individual's tolerance for discomfort, and the assumed duration of ventilator assistance – see ref. (321) for review of the pros and cons. The skill and experience of the nursing staff are also important factors for successful NIV.

Targeting tidal volumes (see also Table 4-2).

Experiences based on positive pressure ventilation of individuals with insufficiency of the respiratory muscle force but essentially normal lungs (e.g. poliomyelitis patients, development of atelectasis during general anesthesia) in the 1950-1960-ties led to recommendations to (322). Such tidal volumes also felt more satisfactory in awake machine-ventilated patients (323). Atelectasis is also common in mechanically ventilated patients with acute respiratory failure, a strategy of using high tidal volumes was therefore also recommended for such patients in the 1960-1970-ties (324).

Patients with ARDS have a significantly reduced volume of aerated lung tissue (low FRC). The use of such tidal volumes could overextend the still-ventilated lung tissue and cause further damage to the already injured lungs, such high tidal volumes are therefore no longer recommended (see "baby lung concept" below). A much-cited paper (18) reported the results of a study comparing the effect of ventilating ARDS patients with tidal volumes of 6 or 12 ml/kg on

morbidity and mortality; the lower volume alternative reduced the mortality significantly. It is important to realize, however, that the study did not establish that 6 ml/kg is the most suitable tidal volume for all patients and that the results may not be valid for patients with other types of respiratory failure.

Ventilation of the ARDS lung.

The "baby lung" concept (325) is based on computer tomography (CT) imaging of the lungs of ARDS patients, showing that most of the dependent parts of the lungs of such patients contains very little gas. As the aerated (and ventilated) lung volume represented only a small part of the normal lung volume, the aerated part was comparable to the volume of a baby lung (326). Thus, normal ventilation volumes could overinflate and damage the part of the lung still being ventilated and participating in gas exchange.

Further investigations showed that when such patients were turned to the prone position, the previously non-aerated part could become aerated while the previously ventilated part became less- or non-aerated. Thus, in the lungs of ARDS patients where the source of pro-inflammatory agents was extra-pulmonary and the edema evenly distributed, the weight of edematous pulmonary tissue compresses the most dependent part of the lung to a degree where normal airway pressures are insufficient to keep the airways open ventilate the lung. As the fluid content of the lung tissue shifted with gravity conditions, the baby lung was also called a "sponge lung" (327).

Regardless of whether the non-functional part of the lung is anatomically fixed (as in pneumonia) or its location changes with body position (as in generalized increase in microvascular permeability), the realization that tidal volumes were distributed to a much smaller volume of lung tissue than in normal lungs had an important impact on the ventilation strategy in ARDS patients (se below for more details).

CONTROLLED VS ASSISTED VENTILATION

Today's modern intensive care ventilators can be set to a variety of alternative modes of ventilation, reflecting the increased focus on the role of the ventilator as a means for *assisting* the patient's spontaneous ventilation instead of exerting full mechanical control of the ventilation. Also, there is an increasing focus on non-invasive ventilation (see above), avoiding the complications of invasive interventions (e.g. intubation and tracheostomy) whenever possible.

Qualified medical personnel are familiar with performing controlled manual ventilation; experienced practitioners also manage manual assistance of a patient's breathing fairly well. Modern ICU ventilators offer a wide variety of options for both controlled and assisted ventilation modes, as well as for settings of various limits, alarms, and automated correction of the configuration of the inspiratory function of the ventilator. Optimal utilization of this variety of options requires both technical and pathophysiological insight as well as clinical experience; the modes outlined below are some of the most common, but do not comprise *all* alternatives.

The benefits of the various modes, as to morbidity, mortality, patient experience, and long-term pulmonary dysfunction are often not well documented. Enthusiastic groups often report a beneficial effect of the modes they champion in smaller studies;, the same results cannot always be confirmed in larger, multicenter studies. Assisted ventilation is often the first choice for many groups of respiratory failure patients who do not need heavy sedation or large doses of analgesics. Regardless of whether assisted or controlled ventilation is chosen, the targeted tidal volume and their frequency (i.e. the ventilation minute volume), level of PEEP, peak airway pressures,

etc. must be chosen with respect to both the severity of the respiratory failure, the degree of hypoxemia *per se* and other individual factors. There are probably no ventilation modes that will prove optimal for all types of patients under all circumstances; algorithms that will be beneficial for the majority of patients in one type of respiratory failure may not suit every patient.

ASSISTING THE PATIENT'S SPONTANEOUS VENTILATION.

The ideal way to support lung function in awake or lightly sedated ARF patients would be ventilation modes that make it possible to

- Ensure that the mechanical inspiratory support from the ventilator is fully synchronized with the patient's breathing.
- Monitor tidal- and minute volumes continuously, and automatically make corrections in the mechanical support to maintain target values for these parameters.
- Configure the flow rate during ventilator inspiratory support continuously to avoid the use of tidal volumes and airway pressure levels that may cause lung damage.
- Keep the airway pressures during the whole ventilator cycle above the ambient, at levels that maintain the total gas exchange surface as normal as possible, *and* at the same time minimize the negative circulatory effects of increased airway pressure.

Modes for assisted ventilation can roughly be divided into three categories:

Pressure or volume support ventilation (PSV, VSV), in which each inspiratory effort by the patient triggers a pressure increase in the inspiratory limb of the ventilator circuit; the inspiratory flow from the ventilator then continues until the airway pressure *or* the tidal volume *or* the flow rate reaches a pre-set level (fig. 4-38).

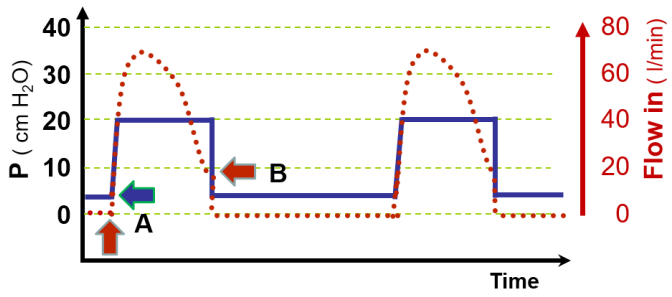

Figure 4-38. *Pressure support ventilation; pressures shown as solid blue lines, flow as dotted red lines. Triggering of a new inspiration* **(A)** *starts when either a reduction in circuit pressures (blue arrow) or start of inspiratory flow (red arrow) is detected by the ventilator sensors. When the flow is reduced to a pre-set percentage of peak inspiratory flow* **(B)***, inspiration stops and the expiratory valve opens.*

The triggering can be set to detect ***i)*** a certain reduction in the circuit pressure below PEEP, "pressure triggering", or ***ii)*** a change in circuit gas flow when the patient starts an inspiration "flow triggering". ***iii)*** a third method utilizes sensors that detect the electrical activity of the inspiratory muscles (see also synchronization below).

Transition to the expiratory phase occurs when the inspiratory flow falls to a certain percentage of the peak inspiratory flow – typically 25%, but can be set individually. A lower percentage results in a longer inspiration phase. This mode functions well in most patients whose strength of inspiration is only modestly attenuated and is especially valuable during the weaning off the ventilator. It requires, however, a sufficient frequency of spontaneous inspiratory efforts.

Synchronized intermittent mandatory ventilation (SIMV) is a variation of this mode, it has a built-in safety net that triggers insufflation of a preset T_V from the ventilator if no spontaneous ventilation is detected within a preset period. If the patient make no attempts to breathe, this mode functions a type of controlled ventilation with a low insufflation rate.

Biphasic ventilation support (BiPAP, BiLevel, etc. (designation varies, unfortunately, between the manufacturers of different ventilator brands). In this mode, the patients breathe spontaneously in a CPAP mode (see above), but the CPAP level alternates between two different pressures that can be set independently (fig. 4-39). The ventilator switches between the two pressure levels at a pre-set number of times during a minute; each time the level of CPAP changes, there is a deeper inspiration or expiration which increases the exchange of the alveolar gas. This helps to maintain alveolar PO_2 and control the CO_2 levels in the blood. If the patient does not breathe spontaneously, this ventilation mode becomes the same as in pressure-controlled ventilation (see below); the upper pressure level becomes the peak inspiratory pressure and the lower level becomes the PEEP.

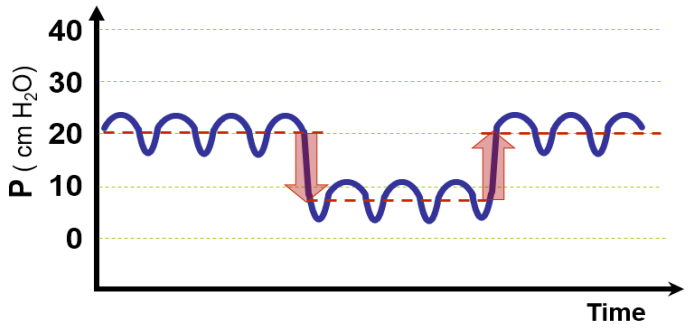

Figure 4-39. *BiLevel ventilation. CPAP at two different levels; each shift in level constitutes an additional ventilation with a larger V_T. If no spontaneous ventilation occur, this mode is similar to pressure controlled ventilation (see below).*

Airway Pressure Release Ventilation (APRV). In this mode, the patients breathe spontaneously in a CPAP mode set at a high pressure level (typically 20-25 cmH_2O) which keeps the alveoli expanded with an optimized alveolar-capillary surface. To facilitate both the alveolar air supply of fresh O_2 and the elimination of CO_2, the expiration valve opens for a short period (typically 0.6 -0.8 sec) at preset intervals, which reduces the total gas volume in the lungs without allowing time enough for the alveoli to collapse. After this expiration period, re-establishing the high pressure supplies fresh inspiratory gas to the alveoli (fig. 4-40). If the patient does not breathe spontaneously, this mode becomes an extreme form of inverse ratio pressure-controlled ventilation (see below), where the alveolar areas are kept expanded at all times and the short expiration/inspiration shifts provide enough renewal of the gas in the alveolar space to maintain P_AO_2 and P_ACO_2 at a satisfactory level. There is no standardized way to set the various parameters involved; recent reviews outline the most common settings and procedures (328, 329).

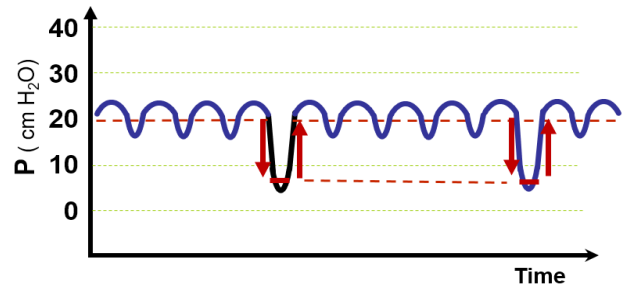

Figure 4-40. APRV *in spontaneously breathing patient. Note the similarity to BiLevel (fig 4-37), except for the very short period of pressure release that do not allow the peripheral airway pressures to reduce significantly.*

CONTROLLING THE VENTILATION.

Setting tidal volumes and frequencies: "Volume Control".

This mode is simple and reliable in the acute phase, and insufflate the lungs with the desired T_V even if the lung compliance and airway resistance changes. For those not familiar with mechanical ventilation devices, it is the mode most similar to manual ventilation and therefore easy to understand. If the peak airway pressure becomes higher than the upper limit set by the medical personnel, modern ventilators not only sound an alarm but may also abort the insufflation, only part of the preset T_V is then delivered. Therefore, this mode may not be optimal in severe bronchospasm (see Asthma below) *or* for prolonged ventilation in all types of patients.

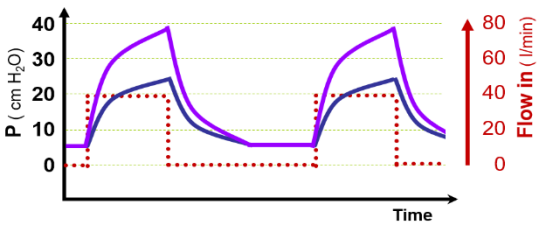

Figure 4-41. *Ventilation with constant volume control and PEEP=5 cmH_2O. Dashed red line indicate flow rate, blue line the resulting airway pressures in the upper airway. Violet line indicate increased pressures in lungs with decreased compliance ("stiff lungs").*

The **airway pressures,** as measured in the ventilator circuit by most ventilators, become a function of the **tidal volume** and **inspiration time** settings, the **compliance** (not only of the lungs but also of the thorax and the abdominal contents), and **airway resistance** (fig. 4-41) in the lungs. The pressures in the *upper* airways may not be representative of pressures in the *lower* airways (i.e. the alveolar distending pressure). These can be estimated by performing an end-inspiratory hold (i.e. a pause where both the inspiratory and expiratory valves are closed, see also below).

Modern ventilators, where **tidal volumes** and **inspiratory time** (usually set as time in seconds or as a percentage of the total cycle – breaths per minute) are set by the medical personnel, can deliver a **constant** gas flow rate, *or* a **decelerating** rate of flow for a defined period (fig. 4-42). The effect of decelerating flow is a faster rise in pressure, which may be beneficial when the lungs contain large areas of slowly expanding alveoli; decelerating flow may be envisioned as a mode in between constant flow and constant pressure (see below) ventilation. At the end of the set inspiration phase, an outflow valve opens and passive expiration is allowed during the rest of the ventilation cycle. A PEEP valve in the outflow part of the machine circuit prevents the airway pressures to become equal to ambient pressure at end expiration.

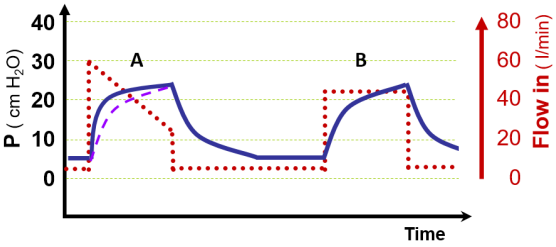

Figure 4-42. *Comparison of decelerating flow (A) with constant flow (B) on upper airway pressures. Note that the peak pressure in* **A** *is achieved earlier (and thus last longer) than in* **B**.

Older mechanical ventilators delivered the set tidal volumes regardless of whether or not the patients attempted to breathe spontaneously. To avoid asynchrony between machine and patient breathing, patients were usually heavily sedated and sometimes curarized. An inspiratory pause (a short end-inspiratory hold) was often employed; the rationale was to create a short period where the inspiratory gas became more evenly distributed before expiration began. Also, the difference between peak pressures and pressures at the end of the pause

gave a rough indication of the relative importance of airway resistance versus the combined lung/thorax/ abdomen compliance (see above). In modern ventilators, inspiratory efforts trigger a new insufflation, and a safety valve prevents the build-up of high airway pressures (see synchronization below).

Setting the insufflation pressures and frequencies: "Pressure Control.

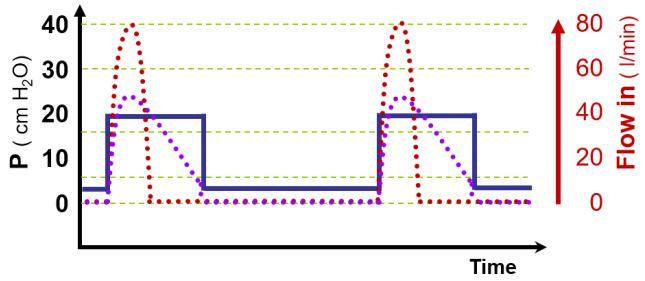

Figure 4-43. *Constant pressure ventilation. Solid blue line represent upper airway pressure, dotted lines inspiratory flow: lilac line represent flow with normal compliance, red line the flow pattern in lungs with low compliance.*

In this mode, the ventilator starts each inspiration by delivering a gas flow at a rapid rate until the desired airway pressure is reached. The flow rate is thereafter reduced continuously to maintain constant pressure during the rest of the inspiratory phase. An option is usually to set a gradual rise in flow to a maximum during the first 5-10% of the inspiratory time, which often feels more natural for awake patients. The **inspiratory tidal volume** becomes a function of the **applied pressure,** the **inspiratory time**, **compliance** (lungs/thorax/ abdomen as above), and **airway resistance** (fig. 4-43).

If the latter parameters change (e.g. change in tone of bronchial muscles, position changes), tidal volumes also change; pressures must then be adjusted if a constant volume is required (e.g. in patients with increased intracranial pressures, where deviations from the targeted P_aCO_2 levels may have deleterious effects). Advanced ventilators may be set to adjust insufflation pressures automatically within a given range of pressures to keep the tidal volumes stable, resulting in a volume-controlled and pressure-regulated mode.

Synchronization between patient and ventilator.

In patients with a strong respiratory drive (e.g. acidosis, hypoxemia, agitation, pain) or with a strong cough, a state of dys-synchrony between the patient and ventilator may occur. This may have two types of consequences: *i)* efforts to start an inspiration when both valves are closed may result in substantial negative airway pressures, *and ii)* if the patient tries to expire actively during a ventilator inspiration, the airway pressures will increase. Both are unfortunate, as negative pressures favor edema formation and atelectasis and very high pressures may cause lung damage.

Modern ICU ventilators are equipped with synchronization functions, where the ventilator senses the patient's inspiratory efforts and opens the inspiratory flow valve in response to inspiratory efforts, they also open the expiratory valve in response to sudden increases in airway pressures.

Attempts to inspire can be detected in many ways; modern ICU ventilators utilize three different methods to sense an inspiration attempt:

- By detecting a decrease in airway pressure (usually detected as changes in ventilator circuit pressure) during the start of inspiration (*pressure trigger*). This functions well in most patients but not in patients with only feeble attempts at inspiration.
- By keeping a continuous and constant low flow of gas through the circuit during the expiratory phase, and interpreting a sudden reduction of the flow as the start of a spontaneous

inspiration (*flow trigger*). This method is generally more sensitive than pressure triggering, but leaks (in the ventilator circuit, or in the seal of tubes or cannulas) can be misinterpreted as inspiratory efforts by the ventilator sensors.

- By detecting the electrical activity in the diaphragm at the start of an inspiration attempt as a triggering signal (*Neurally Adjusted Ventilator Assist* – **NAVA**) (330). This method is the most sensitive, but also the most prone to dysfunction due to electrical disturbances.

CHOOSING THE CORE PARAMETERS

THE TIDAL VOLUMES

Physiological tidal volumes during spontaneous ventilation.

At rest and during quiet spontaneous breathing, the tidal volumes of normal persons vary with body size; the mean resting value of a 70 kg person is about 500 ml, i.e. about 7 ml/kg body weight. During maximal exertion, the tidal volumes may reach 50-70 ml/kg for a short period. Continuous use of tidal volumes higher than the resting volumes *during positive pressure ventilation* of *patients with acute respiratory failure* may, however, have negative effects (see below).

Tidal volume recommendations during positive pressure ventilation in ARDS patients and others.

The amount of lung tissue (i.e. the number of alveoli) that are open to ventilation in severe ARDS is severely reduced by atelectasis and alveolar edema, which means that insufflating tidal volumes that expand normal lungs with relatively low transpulmonary pressures result in much higher pressures when the alveolar area still open to ventilation is reduced. The FRC in patents with severe ARDS is typically in the 1-liter range (331, 332). These higher pressures would then over-extend the still functioning alveolar areas (see also Baby lung concept above) and injure inflamed lung tissue further.

There are no settings proven to be ideal for all patients. The much-referenced ARDS network recommendations of 6 ml/kg ideal weight and maximum 30 cmH_2O of airway pressure (18) were shown to be superior to a strategy of using a tidal volume twice as large (12 ml/kg) in ARDS patients, i.e. using volumes that were previously recommended for atelectasis prevention in persons with essentially normal lungs (see above). Patients that, for various reasons, were excluded from the study and received tidal volumes judged clinically appropriate by the medical staff at

	MALES	V_T, ml/kg IBW				FEMALES	V_T, ml/kg IBW			
Height,cm	≈ IBW,kg	3 ml/kg	4 ml/kg	6 ml/kg	8 ml/kg	≈ IBW,kg	3 ml/kg	4 ml/kg	6 ml/kg	8 ml/kg
140	39	116	154	231	308	34	102	136	204	272
150	48	143	191	286	382	43	130	173	259	346
160	57	171	228	341	455	52	157	210	314	419
165	62	185	246	369	492	57	171	228	342	456
170	66	198	264	397	529	62	185	246	370	493
175	71	212	283	424	566	66	199	265	397	530
180	75	226	301	452	602	71	212	283	425	566
185	80	240	320	479	639	75	226	302	452	603
190	85	254	338	507	676	80	240	320	480	640
195	89	267	356	535	713	85	254	338	508	677
200	94	281	375	562	750	89	268	357	535	714
210	103	309	412	617	823	98	295	394	590	787

Table 4-2. *Tidal volumes, relative to height and idealized body weight (IBW), within the limits recommended by various authors for ARDS patients.*

the time of investigation, had, however, a mortality very similar to those that received 6 ml/kg (210).

It is important to realize that all patients that need mechanical ventilation do not have ARDS and that the rules that govern the ventilation of such patients are not necessarily applicable to all types of patients. In those with intense bronchospasm, achieving even tidal volumes of 3 ml/kg may be impossible if a maximum limit of 30-40 cmH_2O peak airway pressures is applied. It is, however, far better to employ, and accept, higher pressures from a ventilator in such patients instead of continuing manual ventilation, where the true airway pressures are difficult to estimate and the resulting tidal volumes are unknown (see also Asthma attacks below).

SETTING THE F_IO_2.

As soon as reliable measurements can be carried out, the F_iO_2 should be titrated with a goal of keeping the S_aO_2 in the 92-98% range, depending on *i)* the severity of the condition, *ii)* the Hb levels, and *iii)* the estimated circulatory capacity. In patients assumed or known to have chronic hypoxemia and/or hypercarbia and thus usually have a high Hb level, the goal could be in the 88-92% range, provided circulatory stability.

Choosing the inspiration:expiration (I:E) ratios during controlled ventilation.

In most patients where both arterial oxygenation and PCO_2 control can be maintained with a F_iO_2 < 0.40-0.50, PEEP < 8 cmH_2O, and a peak airway pressure below 30 cmH_2O, the I:E ratio is usually set close to 1:2 (similar to the pattern of normal spontaneous ventilation). With a ventilation frequency of 15 breaths per minute (bpm), the duration of each inspiration is then 1⅓ seconds. In patients with severe oxygenation or ventilation problems, changing this ratio may result in better alveolar (and thus arterial) oxygenation (see inverse ratio ventilation below).

Bronchoscopy during mechanical ventilation.

When a normal bronchoscope is introduced through tubes of normal or small diameter (≤ 8.0 mm), the airflow resistance in the tube lumen will increase greatly, since the resistance is inversely proportional to the radius raised to the fourth power: $\mathbf{R = 8nl/\pi r^4}$ (see also Apx). In assisted ventilation mode, patients may have problems with maintaining the tidal volumes and experience a feeling of suffocation; converting to controlled ventilation and deeper sedation before the procedure is therefore recommended. Disconnecting the tube from the ventilator circuit before bronchoscopy to insert an air-tight bronchoscopy adaptor leads to loss of PEEP during the period of disconnection, which may result in small airway collapse in patients with severe respiratory failure ("PEEP-dependent" patients).

Planned short-term disconnection

A suggested procedure for a 3-10 sec disconnection of the patient from the ventilator in marginally oxygenated and PEEP-dependent patients may be:

- Preoxygenate (i.e. F_iO_2=1.0) for at least 5 minutes before disconnection.
- If the patient is intubated and the tube is long enough, the simplest way to retain PEEP and oxygenation is to cross-clamp the tube at end insufflation during the changing of equipment.

If the tube is too short for cross-clamping, or the patient has a tracheostomy tube, the following procedure can be employed:

- A self-expanding bag with a PEEP valve (set to the same PEEP as the ventilator) and the reservoir should be filled with 100% O_2. Let the reservoir fill with O_2, squeeze the air out of

the bag, and then let the reservoir fill with O_2 again. This should be repeated 4-5 times. The bag and reservoir will now contain almost pure O_2.

- When the respirator tubing is disconnected, the ventilation bag should be connected immediately to the cannula/tube. *Compress the bag and keep it compressed* ("inspiratory hold") during the period before reconnecting the ventilator, then perform a recruitment maneuver (see below) after reconnection.

Ventilator settings during bronchoscopy and suctioning.

The pressures recorded by the ventilator (i.e. the pressures within the ventilator circuit) during bronchoscopy do not reflect the pressure in the lower airways, switching to manual ventilation during the procedure may lead to greater loss of PEEP during suctioning than if mechanical ventilation with properly set trigger function is continued (333).

Inspiratory phase.

During **volume-controlled ventilation**, the pressures in the respiratory circuit increase. The tidal volumes will be maintained if the pressure in the tubing does not exceed the set upper limit, but decreases if this limit is exceeded. In the worst case, tidal volumes may fall below the anatomical dead space (which is smaller than normal when endotracheal or tracheostomy tubes bypass part of the upper airways), after which very little fresh O_2 reaches the alveolar space.

Manual ventilation is used in many instances to avoid decreasing tidal volumes during the procedure. It functions in principle like volume control but without the volume restriction inherent in an upper-pressure limit.

In **pressure-controlled ventilation**, the tidal volumes will fall because of increased resistance. The alveoli stay expanded; the reduced tidal volumes during a short bronchoscopy have modest consequences for either P_aO_2 or P_aCO_2 (334). In most patients, these changes are within the acceptable range.

Expiratory phase.

The lungs empty against increased resistance in the tube (danger of increasing "intrinsic PEEP", a danger of pneumothorax if increased out of control). The peak pressures in the airways (and the "intrinsic PEEP") will increase with the magnitude of tidal volumes, but can never exceed the set peak pressures from the ventilator.

Consequences: with a tidal volume of > 200-300 ml and intrinsic PEEP, oxygenation will often be preserved (pulse oximeter must always be connected). PCO_2 will usually rise, but remain within acceptable limits (by 1-3 kPa or 7-20 mmHg) if the procedure takes only a few minutes. Caution must be exercised in patients who are already severely acidotic and/or hypermetabolic.

Problems and complications during positive pressure ventilation.

Unintended high airway end-expiratory pressure (auto-PEEP).

The lungs of patients with COPD are characterized primarily by uneven ventilation of different lung sections and by a heterogeneous increase in airway obstruction. The obstruction is usually most pronounced during expiration. Even during spontaneous ventilation, many patients have some degree of "air trapping" in which raised pressure in peripheral areas of the lungs (mainly in hyperinflated alveoli) compresses more proximal airways during expiration. In such situations, there are alveolar areas where expiration is incomplete and still have a positive pressure when new inspiration is initiated. The pressure in the alveoli and small distal airways in such lung

sections will then increase, and a positive end-expiratory pressure above the PEEP set on the respirator or CPAP system builds up in these areas.

This excess pressure is often called "auto-PEEP" or "intrinsic PEEP", to distinguish it from the PEEP measured outside the teeth or in the ventilation circuit of the respirator. Auto-PEEP should be suspected in all patients where end-expiratory flow does not reach zero before the next inspiration starts. In some patients, such an un-intentional PEEP increase may improve the oxygenation of the blood significantly by increasing the alveolar surface. On the other hand, overexpansion of small peripheral airways increases the risk of pneumothorax and other types of lung damage (see above). This problem is often seen in *asthma patients* with massive bronchospasm, and may also occur in patients suffering from smoke injury in which the airways have not been cleaned of particles by bronchoscopy (see also ventilation of patients with bronchospasm below).

Unintended hypo- or hyperventilation

The compliance of the lungs and airway resistance may change as a result of positive pressure ventilation *per se*, drug therapy, and changes in position. Such changes will alter the ventilation volumes when pressure-controlled ventilation is used. Especially in patients with severe bronchospasm, the use of pressure-controlled ventilation set stringent demands for the monitoring of expired tidal volume and blood gases, as reduced airway resistance in response to therapy may lead to dangerous overexpansion of peripheral small airways. End-expiratory CO_2 may correlate poorly with P_aCO_2, but substantial changes nevertheless show that the ventilation pattern is changing. The medical personnel must be prepared for rapid adjustment of the pressures following tidal volume changes.

Mechanical complications

Pneumothorax is a common complication of intermittent positive-pressure ventilation. The clinical signs are decreasing oxygenation and falling expiratory volume, often accompanied by a fall in blood pressure, increasing airway pressures, and increased central venous pressure. Pneumothorax is particularly likely to occur in patients with significant expiratory airway obstruction accompanied by high auto-PEEP (see above) in part of the lungs.

Accidental extubation/decannulation is a feared complication in patients with poor pulmonary function and reduced FRC and thus a reduced reservoir of O_2 in the lungs, such patients may develop life-threatening hypoxemia in less than a minute. Accidental extubation is usually easy to detect in supine patients but may be less obvious in the prone position. In tracheotomized patients, a dislocated cannula may remain in the pre-tracheal channel while the orifice is located outside the trachea. This may be difficult to detect visually but should be suspected when expired volumes become very small despite high inspiratory pressures. In addition to hypo- or non-ventilation *and* rapidly developing hypoxemia, such situations can also give rise to severe subcutaneous and mediastinal emphysema.

ADDITIONAL OPTIONS FOR PATIENTS WITH SEVERE HYPOXEMIA.

Inverse ratio ventilation.

One way to keep more alveoli open and thus participating in gas exchange is to maintain a positive distending airway pressure for as long as possible during the ventilation cycle. If inspiration is set to last for 50% or more of the ventilator cycle, such ventilation modes are usually called *inverse ratio* modes (fig. 4-44). The expiratory phase may then become too short for the

pressure in "slow" alveolar compartments to fall to PEEP levels, i.e. the expiratory flow does *not reach zero* before initiation of the next inspiration (see auto-PEEP above). The alveoli may then stay open and participate in the gas exchange during the whole ventilator cycle. The negative side of such a strategy is that *i)* alveolar areas supplied by narrow airways may remain expanded before initiation of a new inspiration and thus be continuously over-expanded, and *ii)* a negative effect of positive airway pressure on the circulation in many patients (see Part 3-1).

Prolonged inspiratory hold (recruitment) and high PEEP.

In spontaneously breathing anesthetized patients, low tidal volumes lead to the creation of atelectasis; hyperinflating the lungs at the end of anesthesia to reverse this process can increase the P_aO_2 substantially (335). Also in patients with ARF, especially those with ARDS, part of the pulmonary shunting may be due to the formation of atelectasis. Opening up atelectatic areas, and preventing the formation of new ones, is important for arterial oxygenation; on the other hand, using airway pressures of a magnitude that can be expected to be effective is associated with lung damage and negative effects on the circulation. The use of hyperinflation strategies should therefore be limited to patients where increased alveolar atelectasis represents an important aspect of the oxygenation problem.

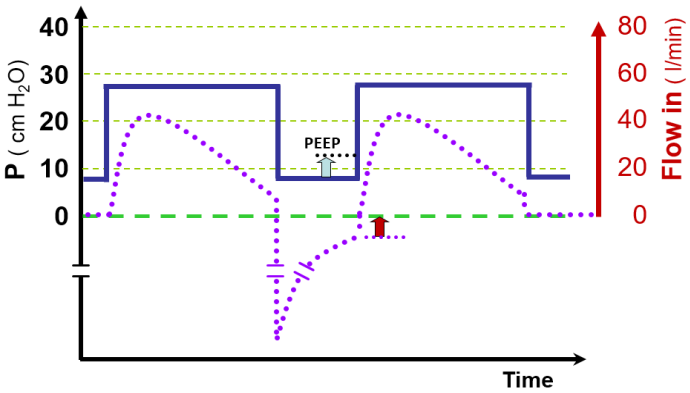

Figure 4-44. *Inverse ratio ventilation (2:1) in pressure controlled mode. Blue line represent airway pressure, dashed lavender line represents airflow. If flow does not reached zero at end expiration (red arrow), the pressures in some of the peripheral lung areas is still higher than the set PEEP (light blue arrow) (auto-PEEP).*

Recruitment procedures tests whether atelectatic areas can be recruited by applying a prolonged inspiratory hold *or* gradual increases in peak airway pressures (336). The logical follow-up in those with a positive response (i.e. increased oxygenation – increased lung compliance) is to increase the PEEP to prevent atelectasis from becoming re-established. There is, unfortunately, no standardized procedure for recruitment – both the magnitude of applied airway pressure and the duration of the hold is important for the effect, and which procedure proves successful, probably varies between individuals and the state of their pulmonary pathophysiology. Most animal and human studies of ARDS have used ventilation where the PEEP is increased in a stepwise fashion (337, 338, 339) up to very high pressures (peak pressure up to 60 cmH_2O, PEEP up to 45 cmH_2O); in studies of anesthetized patients being ventilated during surgery, an inspiratory hold has also been utilized (340, 341).

The author has used an inspiratory hold for 30 seconds x 2, with about 30 seconds of ventilation interposed, and pressures in the 30-40 cmH_2O range as a simple test of whether easily recruitable atelectatic areas are part of the oxygenation problem. During such a procedure, the S_pO_2 often decreases due to the negative effects on the circulation (i.e. an effect of decreased S_VO_2 in low V/Q alveolar areas, see above); the C.O. of some patients, judged clinically to be hemodynamically stable prior to the procedure, can be temporary reduced by as much as 50-65% (342). The

true effect of such procedures on pulmonary oxygenation can thus be observed only *after* re-stabilization of the circulation, usually 1-2 minutes after termination of the procedure.

If a recruitment procedure does *not* increase P_aO_2 or decrease compliance, repeating it later during the same 24-hour period can be considered futile unless procedures like bronchoscopy or other interventions involving temporary loss of positive airway pressure have occurred – if so, and the procedure/incident resulted in decreased P_aO_2, a recruitment procedure can be repeated. The role of recruitment maneuvers and titrated PEEP increase have recently been reviewed (343); the conclusion was that they may represent an increased risk in patients with mild to moderate ARDS but are probably beneficial in severe ARDS. As the percentage contribution of atelectatic – but recruitable – areas that contribute to a low P_aO_2 is unknown in most patients, the effect of recruitment on the individual patient is hard to guess before trying.

Prone positioning.

Prone position (see also ARDS above) may shift the tissue edema when the patient is turned prone (is "proned"), its effect on lung function is primarily an anti-atelectasis maneuver, but a reduction of interstitial and alveolar edema may also occur. It may produce dramatic improvement in oxygenation in many, but not all, ventilated patients with ARDS. The dorsal-caudal part of the lungs is most prone to atelectasis development during mechanical ventilation in the supine position, even in persons with normal lungs (see above). In those with pulmonary tissue edema, this tendency is accentuated (fig. 4-45). The procedure is resource-intensive; a minimum of three, or probably safer for heavier patients, five (344) persons is usually considered necessary for safe turning of intubated or tracheotomized patients from supine to the prone position.

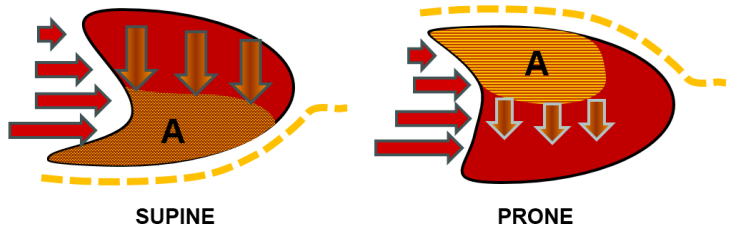

Figure 4-45. *Effect of prone positioning on oedematous areas with widespread atelectasis formation. When the pressure from the abdominal contents and oedematous lung tissue decrease, atelectatic areas may expand and become ventilated again.*

The duration of the prone position period seems to be a critical factor. In an early study in which the patients were proned for six or more hours, a positive effect on oxygenation was observed but this failed to translate into an effect on mortality (345). Later studies, with prolonged prone periods to about 20 hours (346) or 16 hours (192) showed, however, increased survival of the proned group for patients with severe ARDS. A meta-analysis of the various studies on proning concluded that at least 12 hours of proning seems to be necessary to achieve increased survival (347); a recent retrospective study of Covid-19 patients concluded that >24 hours was optimal (348). The main disadvantages of proning are *i)* the manpower resources necessary for safe turning, *ii)* dislocation of endotracheal tubes and tracheostomy cannulas are more difficult to detect and be rapidly remedied, also, *iii)* local tissue ulcerations due to localized pressure points may be established before the danger signs are observed.

Control of body temperature.

Increased temperature leads to increased oxygen consumption, which lowers the mixed venous O_2 content if the C.O. does not increase by the same percentage. In patients with a high shunt

fraction, this will reduce the P_aO_2 and S_aO_2 (see above). High body temperatures should therefore be avoided in life-threatening pulmonary failure. In theory, moderate hypothermia (34-35°C) may be favorable in such situations, but there is little well-documented evidence of the effect of such intervention on survival.

Patients with severe asthma and anaphylactic bronchospasm.

In severe obstruction of the lower airways (e.g. bronchospasm, severe asthma attacks), the major problem is the obstruction during expiration. During spontaneous inspiration, maximal inspiratory pressures of 75-100 cmH_2O below ambient pressure (see above) force gas through the obstruction. Even if healthy musicians may create pressures in the upper airways in the same range during expiration (349), expiration is generally the limiting factor and an extended expiratory period is necessary to avoid overexpansion of the alveolar areas.

When respiratory muscle fatigue commences and the patient no longer manages to sustain such pressures, ventilation assistance must be provided. Non-invasive assistance may be sufficient for many patients; in extreme cases, however, when very high inspiratory pressures must be employed, acute endotracheal intubation may be necessary. The anesthetic drugs ketamine and propofol are often the preferred sedation agents under such circumstances, as they may have an anti-bronchospastic effect (350), the evidence for a better clinical outcome is, however, hard to prove (351). Sedation in connection with endotracheal intubation reduces, or abolishes, the effort of the patient's expiratory muscles, which may prolong the expiratory phase further. Inhalation of ethyl ether vapor was tried as a last resort with some success during the 60-70 ties, its flammability limits, however, the safe use of this agent. Other anesthetic gases like halothane, enflurane, and isoflurane have also been used in attempts to reduce intense bronchospasm (reviewed in ref. 352). Administration of helium-oxygen mixtures, that have a lower gas viscosity than air-oxygen mixtures, have been tried in both spontaneously and mechanically ventilated patients. There are case reports describing improvement in ventilation mechanics with such treatment (353), the effects on lung function, morbidity and mortality are, however, not well documented (354).

Use of extreme pressures during life-threatening bronchospasm.

A few patients with intense bronchospasm cannot be ventilated using the normal ventilator settings considered to be "safe". Attempts to switch from manual ventilation to machine ventilation after intubation may result in all sorts of ventilator alarms going off, aborted inspiration attempts, and, at worst, non-ventilation of the patient. Switching back and forth between manual ventilation and trying mechanical ventilation anew after checking the machine leads to a loss of critical time. Interposing a pressure monitoring device between the bag and the endotracheal tube in such situations revealed that the pressures necessary to ventilate such patients, even with tidal volumes half of normal or less, may be in the 50-80 cmH_2O range (355).

In patients with life-threatening (also called near-fatal) asthma attacks, normal tidal volumes are not possible to obtain by any means. With today's focus on "gentle" ventilation and the specter of barotrauma, most medical personnel will feel uncomfortable when using such pressures from a ventilator. Nevertheless, securing adequate oxygenation of the blood while waiting for the effects of i.v. or inhaled bronchodilating agents must have the highest priority.

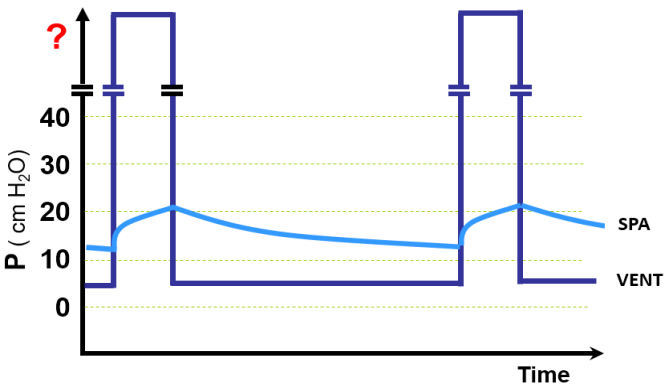

Figure 4-46. *Ventilation of patient with severe bronchospasm. To create long expiration periods, inspiratory periods must be short. Very high pressures in the ventilator circuit (VENT – blue curve) may be necessary, the pressures in the peripheral air spaces (SPA-light blue) is probably much lower. Auto-PEEP will be present; its magnitude may be difficult to estimate as such patients do not tolerate long enough periods of end-expiratory hold.*

During positive pressure ventilation of such patients, the expiration time must be kept as long as possible; a low respiratory frequency (8-10 bpm) and prolonged expiratory time have been recommended (356). The same authors, as well as others, also advocate tidal volumes of 6-8 ml/kg and I:E ratios of 1:3-1:4 (357, 358). In this author's experience, such tidal volumes are impossible to obtain during life-threatening asthma attacks. With a frequency of 8 bpm and an I:E ratio 1:4, the expiratory period is 6 sec, i.e. more than *twice* that in "ordinary" settings. Despite this, the tidal volumes may be in the 180-250 ml range.

The CO_2 will continue to increase; an accompanying respiratory acidosis is unavoidable under such conditions but is usually tolerated as long as critical hypoxemia can be avoided (see above). In desperate situations, with a very low P_aO_2 and where a rightward shift of the HbO_2 curve aggravates the hypoxemia, the acidosis can be ameliorated by i.v. infusions of non-bicarbonate buffers for a limited period (see Part 5-4).

In opposition to the situation in most other patients, the pressures recorded by the ventilator are not transmitted to the alveoli (fig. 4-46), an approximate estimate of alveolar pressures may be obtained by pressing the "end-inspiratory pause" button found on many modern ICU ventilators. The time necessary for getting reliable results in this type of situation may, however, be too long to be safe in a critical situation. Applying the same limitations for peak airway pressures as those recommended for ARDS patients in such situations may lead to a situation where the ventilator only compresses the gas in the dead space during inspiration without supplying fresh O_2 to the alveoli, and the patient dies from severe hypoxemia.

Unconventional ventilation modes: jet ventilation, oscillatory ventilation.

The goal of this ventilation mode is the same as for inverse ratio ventilation and PRV, i.e. to keep the airways expanded by increasing the mean airway pressure in patients with severe oxygenation problems. In patients without spontaneous breaths, there are no tidal volumes in the ordinary sense; the passage of O_2 molecules downwards and CO_2 upwards through the lower airways results from continuous airway turbulence created by short pulses of increased pressure. These may be induced by an *oscillator* (similar to the membrane of a bass loudspeaker) connected to the ventilator circuit (oscillatory ventilation) *or* by a catheter positioned in the trachea through which small volumes are injected with high frequency (*high-frequency jet ventilation*). The principle of jet ventilation insufflates a small tidal volume (30-50 ml) at high speed and under high pressure through a thin cannula or catheter at the rate of 100-500 insufflations per minute. The pressure waves created by oscillation or short jets or gas keep the alveoli distended. In patients with bronchopleural fistulae and major air leakage during intermittent positive pressure ventilation, such ventilation may result in significant improvement of the gas exchange.

The problems with high-frequency jet ventilation and oscillation are that they usually produce an increased CO_2 in the blood and that the criteria for determining the respirator settings are uncertain; the settings for the individual patient must often be found by trial and error. If the outlet of expired air is obstructed, high-frequency ventilation may also create extremely high pressure in the airways and produce an acute positive-pressure pneumothorax. Although both ventilation modes may improve oxygenation in patients with severe lung dysfunction, sometimes dramatically, an improvement in survival has not been proven (359, 360).

DRUGS AND AGENTS IN ARDS TREATMENT.

Effects on the disease process per se.

As ARDS represents an inflammatory process in the lungs, the effect of many anti-inflammatory drugs and agents (e.g. corticosteroids, anti-oxidants, statins, β_2-agonists, neutrophil elastase inhibitors, heparin inhalation, exogenous surfactant, salicylates, etc.) have been investigated. Some of the agents that, on theoretical grounds, could ameliorate the pathophysiological changes in ARDS lungs, have shown promising effects in animal models of ARDS and small patient studies. None of them, with the possible exception of anti-inflammatory corticosteroids (see below) has been proven to have a significant impact on the mortality of ARDS patients in large, high-quality studies; for a summary of such studies, see refs (361, 362, 363, 364, 365).

Agents which may improve hypoxemia by preferential perfusion of the best ventilated alveolar areas.

Some inhalation agents, like nitrogen monoxide gas (NO) and aerosolized prostacyclin (PGI_2), can substantially increase the lung's ability to oxygenate the blood in many, but not all, ARDS patients. Both agents have an important role as physiological vasodilators in the human organism; when they are added to the inspired air, the best-ventilated areas also receive the highest concentrations of the agent. The selective vasodilation of the vessels supplying these areas results in a positive "steal" effect, where more of the perfusing blood is directed toward the alveolar areas with the best ventilation. They may also produce a marked reduction in pathologically increased pulmonary vascular resistance in certain contexts, but this effect is moderate in patients with severe ARDS. Although their effect on gas exchange and pulmonary vascular resistance is well documented, treatment with neither NO nor PGI_2 has been shown to shorten the course of the disease, nor to increase the mean survival rate in multicenter studies of patients with ARDS (366, 367). In patients with severe hypoxemia, such therapies may, however, buy time for other types of interventions to be implemented in selected patients.

Effects of corticosteroids.

This class of anti-inflammatory drugs (e.g. methylprednisolone, dexamethasone, hydrocortisone, prednisolone, etc.) should theoretically be a good candidate for ameliorating the pathophysiological processes involved in ARDS. Inspired by the positive effect reported for pharmacological doses of methylprednisolone in patients with lung contusions (368), clinicians (including the author) have observed that some patients with severe ARDS may improve their pulmonary function dramatically within the first 24 hours after initiation of such treatment. Unfortunately, the majority of patients show little or no change, and prediction of which patients would be responders proved impossible. Concerns about complications associated with such drugs (e.g. decreased infection control, gastric ulceration, reduced wound healing, hyperglycemia, etc.) have limited their use, even if short-term use seems to be fairly safe (369).

Numerous scientific investigations of the effect of corticosteroids in ARDS patients have been carried out, and around three thousand papers (up to 2021) describing original research or meta-analyses have been published. Despite this activity, the role of such drugs in ARDS treatment is still uncertain. The patient outcome in larger studies has resulted in conflicting results (370, 371), and the role of such drugs in ARDS, as well as dosage, when to start and to stop, has been uncertain for many decades (372).

One of the possible explanations for conflicting results is the lumping of ARDS patients with different underlying etiologies (i.e. provoked by agents reaching the alveoli via the airway *or* the blood) in larger studies. The syndrome is not a disease per se, the inflammatory state of the lungs may be caused by airborne microorganisms, microorganisms, and proinflammatory agents from other infectious foci, from aseptic inflammatory diseases, and traumatized or hypoxic tissue (369). The use of corticosteroids seems to be associated with a better outcome in severe ARDS caused by microorganisms (373, 374), and preliminary studies of ARDS in patients with Covid-19 infections indicate an important place for corticosteroid treatment in this disease (375, 376).

Most publications during the last decade seem to be in favor of the use of corticosteroids, and a reduction in the number of ventilator-dependent days as well as in mortality have been reported by investigators conducting large studies (377) as well as after new meta-analyses (378, 379). There is a consensus that such treatment should be given early after the ARDS diagnosis is established; an optimal dosing regime has, however, not yet been definitely established.

Some ARDS patients develop excessive pulmonary fibrosis, a dreaded complication that develops in a sub-segment of ARDS patients and often ends with death after protracted efforts to liberate the patient from the ventilator (198). Corticosteroids have been given late during the phase of ARDS to combat such fibrosis; even if such treatment is associated with a shorter period of mechanical ventilation dependency, there is, presently no evidence that such drug regimens affect mortality (380, 381).

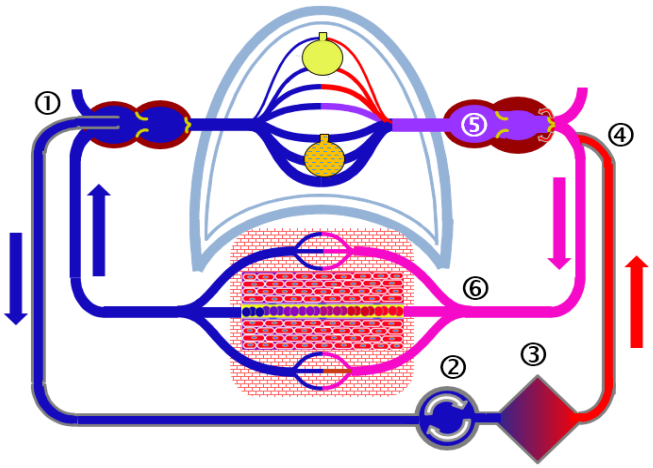

Figure 4-47. *Schematic drawing of a veno-arterial ECMO device. Part of the venous blood returning from the circulation is drained from the right atrium ①, pumped ② through an oxygenator ③ and injected into the upper aorta ④, where it mixes with the blood that has passed through the lungs ⑤. Oxygenation of the arterial blood ⑥ is determined by **i)** the SO_2 of mixed venous blood and **ii)** the ratio of blood flowing through ④ and ⑤.*

Oxygenating the blood outside the organism (ECMO - extracorporeal membrane oxygenation, *also called* **ECLS –** extracorporeal life support**).**

Devices for extracorporeal membrane oxygenation were developed to enable surgery on the heart and large vessels without the need for extreme hypothermia. During such surgery, the beating of the heart can be stopped and the whole blood volume bypasses the heart through a circuit where blood is drained from the right side of the heart, pumped through a membrane oxygenator (which also removes CO_2), and into the arterial system (see also Part 3-4, fig. 3-30). In patients with severe lung and circulatory failure, this

technique (i.e. veno-arterial ECMO) can be utilized to assist both pulmonary and cardiac function (fig. 4-47). Part of the circulating blood is drained from a cannula inserted percutaneously into the right atrium, pumped through an oxygenator, and into a cannula advanced into the upper part of the descending aorta. The C_aO_2 of arterial blood becomes the weighted mean of the O_2 content of the blood passing through the lungs and that passing through the circuit. If the former is 2.5 l/min with a S_aO_2 of 70% and the latter is 2.5 l/min with a S_aO_2 of 100%, the mean S_aO_2 in the blood perfusing the organism is about 85%. Besides the possibility of avoiding life-threatening hypoxemia, the lungs can rest without being exposed to high oxygen concentrations and high airways pressure from the respirator; a healing process is then assumed to be more likely to succeed.

If the circulation is adequate and only the lungs are in failure, a veno-venous ECMO (fig. 5-48) may be used. Venous blood is then drained from a major vein (usually cava inferior), oxygenated, and pumped back close to, or into, the right atrium. If the S_VO_2 is 70%, with a flow of 3 l/min passing by the drainage cannula and entering the lungs, and the circuit flow is 2 l/min with an SO_2 of 100% when leaving the cannula in the right atrium, the SO_2 of the blood entering the lungs is 82%. Even if the whole lung represents a shunt (no alveoli are ventilated), the S_aO_2 of the arterial blood will be 82% - which is low but survivable in a previously healthy organism if failure of the lungs represent a single organ failure. For both techniques, the CO_2 level in the blood can be controlled by adjusting the gas flow through the oxygenator.

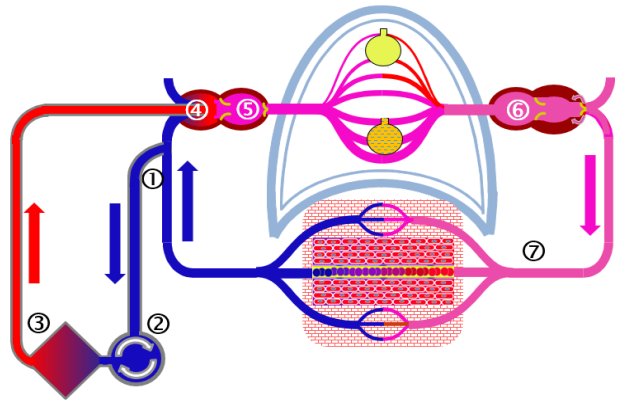

Figure 4-48. *Schematic drawing of veno-venous ECMO device. Venous blood is drained from a major (often femoral) vein ①, pumped ② through an oxygenator ③ before re-joining the blood stream in the right atrium ④. The blood leaving the right ventricle ⑤ is then already partly oxygenated; if the lungs are able to add some further O_2 to the blood, the arterial C_aO_2 (6) may be sufficient.*

The effect of such devices on O_2 supply to the organism may be life-saving in the acute phase, the equipment is continuously improved and their use has increased during the last decades. There are, however, still many complications to the treatment; a long-term beneficial effect on morbidity and mortality in ARDS patients is still moderate to non-existent (382, 383) and criteria for choosing patients who may have the highest potential for benefiting from such treatment are not well defined (384). It should therefore, presently, be restricted to only special circumstances, e.g. in life-threatening hypoxemia in younger persons where pulmonary failure (single-organ failure), possibly combined with reversible circulatory failure, can be considered the major medical problem.

Eliminating CO_2 outside the body (ECLA-extracorporeal lung assist**).**

While a high fraction of the total blood must be oxygenated by the extracorporeal circuit to ensure adequate C_aO_2 in severe hypoxemia, a smaller blood flow is sufficient for eliminating enough CO_2 to allow further reduction of tidal volumes and airway pressures during mechanical ventilation of ARDS patients (385). The flow through the extracorporeal circuit can then be driven

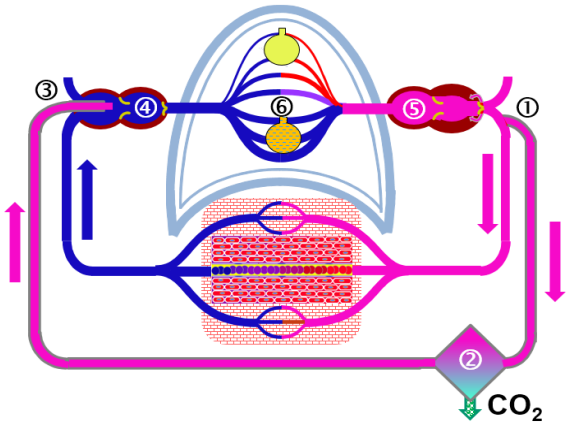

Figure 4-49. *Schematic drawing of a device for extracorporeal removal of CO_2. The arterial pressure drives the flow though the circuit ①, the blood passes through a gas exchanger ② that eliminates CO_2 after which the circuit blood ③ returns to the right atrium ④. Blood entering the left atrium ⑤ must still be oxygenated by the lungs ⑥.*

by the arterial pressure, eliminating the need for a pump (Fig. 4-49). The efficiency of CO_2 removal is related to both the flow through the extra-corporeal circuit and the CO_2 concentration in the inflowing blood (386). Even if the blood flowing through the circuit can be fully oxygenated by the gas exchanger, this flow is limited and it cannot solve the oxygenation problem if the patient has a substantial pulmonary shunt. Also this type of treatment is associated with complications and cannot be a permanent solution; a reduction in mortality has been assumed but has not been proven.

CHOOSING THERAPEUTIC INTERVENTIONS APPROPRIATE FOR THE SITUATION

Weighing risks against benefits in ARF patients may be difficult; there are potential negative effects inherent in any intervention (e.g. O_2 toxicity, O_2 atelectasis, volo- and barotrauma, VILI, circulatory problems) and almost all strategies can be criticized. At any crossroads, however, the *risk of performing a given intervention must be weighed against the risk of abstaining* from it. When judging whether an intervention is justified or not, it is important to discriminate between the options available in various situations; in pre-hospital emergency settings with a lack of background information and limited resources, priorities may be different from those in well-equipped and -staffed emergency- and operating rooms as well as in intensive care units.

Regardless of the setting, in a hyperacute phase with a patient that is on the point of dying of severe hypoxemia *or* a combination of hypoxemia and hypercarbia, almost any intervention that theoretically may improve one or both factors may be justified. As soon as the situation becomes stable, however, and logical assumptions about a diagnosis can be made, a re-evaluation of therapeutic risks and benefits is mandatory,and must be followed by modifications of the initial strategies whenever necessary.

TARGETING P_AO_2/S_AO_2 AND CHOOSING F_IO_2.

- **In emergencies**, before blood gas or reliable S_pO_2 measurements can be obtained, patients who are judged to be in acute respiratory distress and/or circulatory unstable should receive gas with a F_iO_2 as close to 1.0 as possible. The importance of this strategy is exemplified by data shown in fig. 4-12, from a patient treated for acute anaphylactic bronchospasm (387). Advanced devices for administration of O_2 may not be available during the initial treatment phase; an O_2 flow of 15 l/min to a reservoir mask (if available) with a good fit may result in a F_iO_2 of 0.8-1.0 within minutes in most patients with normal minute ventilation. An ordinary open face mask with the same flow may give a F_iO_2 of 0.5-0.6 (see Devices above), large variations may, however, be expected in real-life situations. When reliable S_pO_2 measurements can be obtained, the amount of supplementary O_2 can be titrated downwards if the S_pO_2 is >95% and the possibility of CO intoxication can be ruled out (most devices for measuring S_pO_2 cannot discriminate between HbO_2 and HbCO).

- **In controlled environments after stabilization** (e.g. emergency- and operating rooms, intensive care units). If *Hb* levels and the *capacity for circulatory compensation* are satisfactory, a S_aO_2 of 92-93% should be a reasonable target for patients without localized perfusion problems. If there is a pulmonary shunt of 50% or more, increasing the F_iO_2 has little effect on the P_aO_2 or on the C_aO_2 (see Fig. 4-28). Thus, if increasing the F_iO_2 from 0.35 to 0.7 has only a minimal effect on the P_aO_2, shunting is the main cause of hypoxemia and a further F_iO_2 increase cannot be expected to have much effect on the C_aO_2.

SEDATION AND ANALGESIA DURING MECHANICAL VENTILATION

General considerations.

Having an endotracheal tube in place, and the various procedures often associated with being an ICU patient, can be extremely uncomfortable; many lightly sedated patients afterward remember interventions, especially the suctioning of airway secretions, as very unpleasant procedures. In traumatized and newly operated patients, especially with upper abdominal surgery and thoracotomies, pain from fractures and wounds constitute a separate problem that also needs to be addressed.

The objective of protecting the patient against discomfort caused by an endotracheal tube, situation stress, pain, and the intensive care environment with sedative and painkilling drugs not infrequently conflicts with the need for active training of the respiratory muscles. This problem is especially frequent in fearful patients with a low stress threshold, drug- and alcohol addicts, and patients that develop delirium for various reasons. Benzodiazepines, more potent tranquilizers, or sometimes antidepressant drugs may help; the effect of benzodiazepines may, however, be unpredictable in the elderly, who sometimes become excited instead of sedated. The effect of even small doses of many drugs may last for several days in patients with severely impaired hepatic and/or renal function.

Most conscious patients need deep sedation during elective intubation; for several decades after positive pressure ventilation became common, deep sedation was usually continued during the next hours and days of controlled mechanical ventilation. Sedation was given as intermittent doses of sedatives and analgesics (often morphine), or as continuous infusions of more short-acting agents. The depth of sedation was reduced only when the state of gas exchange and ventilation showed signs of improvement. A serious drawback of this strategy was that the accumulation of drugs, and the time elapsed between discontinuing the agents and the actual wake-up of the patients, were unpredictable. In addition, the possibility of evaluating the patient's cerebral state was very limited in scope.

Morphine, with its combined sedative and analgesic properties, is in many ways an excellent drug for mechanically ventilated patients, many patients do well with patient-controlled ventilator modes even at high doses (up to 10-15 mg/hour after long-term treatment). The duration of the effect of morphine may be difficult to predict; morphine metabolites also have potent sedative and respiratory-depressant properties. The effect is especially protracted in patients with renal failure, where their elimination is delayed in an unpredictable way (reviewed in ref. 388). This, and the specter of drug dependency and abstinence problems, limits its use, and it has largely been replaced by continuous infusions of other, short-acting agents. Under austere conditions, however, with limited availability of both infusion pumps and mode modern drugs, morphine may still be considered a valuable agent; it should not, however, be given as a continuous infusion to renal failure patients.

In certain patient groups (e.g. those with serious head injuries, major trauma with multiple fractures, and life-threatening pulmonary failure), the depth of sedation and analgesia must be suf-ficient to protect unstable patients against unnecessary cerebral excitation, pain, and increased $\dot{V}O_2$ due to increased catecholamine release. In other patient groups, deep sedation is often unnecessary; the discomfort during unpleasant procedures can be minimized by the administra-tion of short-acting sedatives and analgesic agents shortly before they are performed. A change in the sedation strategy was advocated at the beginning of this century (389). During the following decade, several investigators reported that light sedation, especially when combined with daily "wake-up calls" (i.e. daily interruption of sedation to be able to communicate with the patient), may reduce the number of ventilator-dependent days (390, 391). Such procedures make it possible to observe the cerebral state, as well as the neuro-muscular function, of the patient. It also gauges the depth of sedation and makes it easier to decide whether weaning procedures should be initiated.

A regime with no routine sedation (but bolus doses of morphine when deemed necessary), when compared to light sedation with daily wake-up calls, was also found to reduce the duration of mechanical ventilation and ICU care (392). Such a regime failed, however, to show a benefit on 90-day mortality (393). One meta-analysis comparing protocols for light sedation with individu-ally prescribed sedation found that such protocols reduce both mortality, ICU and hospital length of stay, and incidence of tracheostomy (394). Other analyses failed, however, to find any of these differences except for a positive effect on the length of hospital stay (395, 396).

There are probably no sedation regimes that are optimal for all ages and types of patients. Most of the research on light sedation and wake-up calls has studied the effect on predominantly medical patients; conclusions based on such populations may not be relevant for all types of patients. The concept of never employing deeper sedation than necessary during mechanical ventilation, and using bolus doses of analgesics and/or sedatives in connection with unpleasant procedures should, however, be considered valid for all patients. Continuous infusion of an in-travenous hypnotic with a short half-life, e.g. low-dose 2,6-isopropylfenol (propofol, 0.5-3 mg/kg/hour), may be an easy-to-use alternative to other sedatives when initiating a weaning process.

Use of neuromuscular blocking agents.

Neuromuscular blocking drugs are commonly administered during elective endotracheal intuba-tion and are sometimes a necessary therapeutic adjunct to combat asynchrony between patient and ventilator when this leads to ventilation and gas exchange problems. Such agents were commonly used during controlled mechanical ventilation of patients with severe respiratory fail-ure four to five decades ago, reports of generalized muscular weakness after long-term use (critical illness myopathy, reviewed in ref. 397) led to a decline in their use. Such myopathies may, however, occur also in patients who have not received muscle relaxants during their ICU stay, and recent research has failed to find a significant connection between neuromuscular blockers and such muscular weakness when the duration of administration was limited to 48 hours (398, 399). Also, a smaller study did not find any difference between short- and long-term administration of such drugs (400).

On the positive side, the use of such agents in patients with severe respiratory failure has been reported to result in improved gas exchange and reduced ventilator time (401, 402). A possible explanation for a beneficial effect on the P_aO_2 could be a reduced $\dot{V}O_2$ during a neuromuscular blockade, as found in one study (403); this may not, however, be the case in all patients (404).

Administration of neuromuscular blockers during the first 48 hours of mechanical ventilation has also been reported to reduce mortality and ventilator days in patients with severe ARDS (398); a more recent study (405) failed, however, to confirm this result.

A major concern with the use of neuromuscular blockers is the difficulty of estimating whether sedation is adequate, one retrospective study concluded that as many as 18% of patients receiving a long-acting neuromuscular blocker may have experienced a period of insufficient or ineffective sedation (406).

MONITORING DURING MECHANICAL VENTILATION.

When the *level of F_iO_2* and mode of *ventilation support or control* have been decided, the effect of the chosen treatment, not only on pulmonary gas exchange *per se* but also on O_2 delivery (DO_2) and pulmonary mechanics, must be controlled and preferably continuously monitored.

The **primary goals** of such monitoring are

- To give **rapid feedback** about whether the chosen F_iO_2, ventilation mode, tidal volumes, airway pressures, I:E ratios, etc. has the desired effect on pulmonary gas exchange and thus on arterial blood oxygenation.
- Gauge the effects of mechanical ventilation settings on **circulatory parameters**, especially on the C.O. As positive pressure ventilation has negative effects on preload and cardiac function in many patients, the DO_2 may decrease *despite* a beneficial effect on P_aO_2 and S_aO_2 *per se*. Monitoring of circulatory parameters are therefore an integrated part of the monitoring of most mechanically ventilated ARF patients, such monitoring is outlined in Part 3-4.
- To give an **early warning** about changes in pulmonary or circulatory function that affects the DO_2 and CO_2 excretion, or ventilator settings or dysfunctions that may cause additional damage the lungs. Acute or subacute changes in P_aO_2 and S_aO_2, especially if accompanied by a fall in ABP and increased CVP, may be due to acute cardiac failure, pneumothorax, and other space-occupying processes within the thoracic cage or the pericardium. In mechanically ventilated patients, a positive pressure pneumothorax may create a critical situation within minutes and require urgent drainage.

The secondary goals of monitoring may be to evaluate

- Changes in **lung mechanics and gas exchange**, which enable rapid adjustments to optimize ventilation patterns to be made.
- The possible **effect of pharmacological interventions** on lung mechanics and gas exchange.
- **Progression of the disease process**, to plan for additional interventions, or for weaning from the ventilator. The progression, or resolution, of the pulmonary dysfunction, can be deducted from changes in the P_AO_2-P_aO_2 difference, the P_aO_2/F_iO_2 ratio, and the relationship between tidal/minute ventilation volumes and P_aCO_2 and/or end-tidal CO_2 (i.e. changes in the alveolar V/Q ratio). Also, a reduction in the airway pressures necessary to maintain the target tidal volume is usually a positive sign.

A tertiary goal of monitoring may be acquiring **data for scientific purposes.**

Tools for monitoring.

These can roughly be classified as either intermittent or continuous. The most important of the intermittent tools is

Analysis of arterial blood gases (i.e. PO_2, PCO_2, and pH), supplemented with measurement of S_aO_2 and Hb (see also Part 5-4), monitors both gas exchange function and C_aO_2. When focusing on the lung gas exchange function, P_aO_2 must be compared to the calculated P_AO_2. When focusing on O_2 delivery to the organism, S_aO_2, Hb and estimated C.O. are the important parameters. Frequent sampling in unstable patients usually requires an indwelling arterial catheter. In well-circulated patients, both PCO_2 and pH in venous blood differ only modestly from those in arterial blood, venous samples can be substituted for arterial *if* the state of oxygenation of arterial blood can be reliably monitored by pulse oximetry.

Imaging techniques.

Chest X-rays, ultrasound examinations, CT scans, etc. are used to detect infiltrates (pneumonia), intrapleural fluid and air accumulation, aeration of various parts of the lungs, etc. Bedside plain chest X-rays are easy to acquire, but have limited diagnostic value; CT scans give much more information, but usually require transport to a CT lab, which always represents an additional risk for severely ill patients.

Continuous monitoring of HbO_2 saturation by pulse oximetry (S_pO_2) can detect changes in pulmonary gas exchange, and give second-to-second information about the oxygen status of the arterial blood. The technique depends on adequate peripheral circulation; it can also be affected by the presence of carboxyhemoglobin, methemoglobin, and various dyes in the blood (see refs. 407 and 408 for a comprehensive list of sources of these types of error). The values measured by this method must always be verified by blood gas measurements in the initial phase.

Continuous monitoring of the CO_2 in the expired, end-tidal gas ($ETCO_2$) is representative of the arterial PCO_2 in persons with healthy lungs. Both ARF, as well as COPD, patients may have large alveolar areas with a high V/Q ratio, the $ETCO_2$ is then substantially lower than the arterial value. The relationship between the $ETCO_2$ and P_aCO_2 for each patient must therefore be established by analysis of arterial CO_2 levels during the initial phase of $ETCO_2$ monitoring for this parameter to be meaningful. Also, changes in the pulmonary and/or circulatory state should lead to a control of the relationship between arterial and end-tidal CO_2.

State of lungs and airways. Modern ventilators offer various options for graphic display of dynamic pressure-volume and flow-volume curves, calculation of compliance, estimation of auto-PEEP, trans-pulmonary pressures, etc. These functions describe the state of lung mechanics, and the relationship between airway resistance and lung compliance, which may help choose PEEP and V_T in individual patients. They also represent important aspects of patient monitoring and give information about the progression of the conditions of the lungs. In addition, modern ventilators are equipped with various alarms that warn about changes in the state of the patient lungs, as well as circuit dysfunction and leaks. Early detection of changes in airway resistance or lung compliance, development of a pneumothorax, etc. enables rapid interventions before the situation becomes dangerous.

Weaning from controlled ventilation.

The weaning process.

Weaning (i.e. the process where a gradual decrease in mechanical support of the ventilation concludes with progression from ventilator dependency to adequate spontaneous breathing) is an integrated part of mechanical ventilation treatment. The respiratory muscles, like any other striated muscles, atrophy when not in use. In addition, a lack of activity coordination between different respiratory muscles may occur after they have been inactive for several days. It is therefore important that a patient in acute respiratory failure starts ventilation in a mode that promotes the use of his/her respiratory muscles, with the ventilator supporting the patient's breathing as necessary, as quickly as possible (see assisted ventilation above).

As soon as oxygenation and circulation are stabilized and the underlying medical problem is identified and remedied (if possible), the feasibility of initiating the weaning process should be addressed at least daily. In patients needing short-term mechanical ventilation support (e.g. after surgery, respiratory emergencies, drug overdose), such evaluation should be done on an hourly basis or every few hours; weaning may than consist only of a short trial of spontaneous ventilation (often employing a CPAP circuit) before extubation.

The requirements for initiating a weaning process vary from patient to patient; e.g. targets for oxygenation and ventilation may differ between patients with acute-on-chronic respiratory failure than those in previously healthy persons with acute respiratory failure. In general terms, the prerequisites for initiation of the weaning process in most patients (409) should be that

- The underlying cause of ARF is resolved or shows significant improvement.
- The pulmonary oxygenation is adequate (e.g. P_aO_2/F_iO_2 > 20-27 kPa (150-200 mm), i.e. > 10 kPa (75 mmHg) at F_iO_2 0.5, and a PEEP not higher than 8 cm).
- The hemodynamic state is stable, and
- The patient can initiate spontaneous inspirations.

In patients who have needed fully controlled ventilation for many days, it is sometimes difficult to get patient-controlled assisted ventilation started. Assuming there are no drug-related or pathophysiological obstacles to spontaneous respiratory activity, failure to get patient-controlled ventilation started may be due to staff impatience. Apnea for more than 30 seconds should not be considered proof of a lack of spontaneous respiratory activity. The fear of respiratory acidosis is usually exaggerated, since the blood CO_2 increase in apnea is a slow process in normothermic, sedated patients (0.6-0.8 kPa/min, see previously). If the patient is pre-oxygenated with 100% O_2 for some minutes before testing for spontaneous respiratory activity, waiting 2-3 minutes for spontaneous ventilation activity to occur is reasonable, provided that the oxygen saturation as measured by pulse oximetry remains above 90% (apneic oxygenation). A surprisingly large number of patients in such a situation may have total apnea for the first 1-2 minutes before the first spontaneous ventilation can be observed. Many of them subsequently establish a satisfactory spontaneous ventilation rate over the next 3-10 minutes.

Weaning methods.

In the 1960-70-ties, weaning usually consisted of intermittent periods of spontaneous breathing with the endotracheal- or tracheostomy tube connected to a T-piece, where humidified gas with a pre-set F_iO_2 was supplied through the afferent limb of the tubing. During the 70-ties, this was

often combined with a bubble trap or a PEEP valve and a reservoir, creating a CPAP system (see fig. 4-33).

With the progressive sophistication of ICU ventilators, a gradual reduction in mechanical support was made possible through the advent of machines with synchronized intermittent mandatory ventilation (SIMV) and pressure- and volume support ventilation (PSV/VSV) functions. Investigators evaluating the relative merits of each method report different findings (410, 411), variations in results may vary not only with the type of patients and their co-morbidity but also with the established routines and experience of the staff. Many modern, sophisticated ventilators have advanced alternatives for patient-controlled assisted ventilation and can be set to start supportive controlled ventilation automatically if the patient's ventilation in assisted mode fails to generate adequate tidal- and minute volumes. The use of such ventilators makes early weaning attempts both easier and safer.

Stress may result in high arterial pressure (afterload increase) and trigger heart failure in patients with marginal cardiac function. To avoid this, potent vasodilators must, if necessary, be administered *before* the patient becomes stressed by the weaning process and develops hypertension. Premature extubation, resulting in a further period of stress, dyspnea, and re-intubation, is experienced as an enormous setback by many patients. Patients that have needed mechanical ventilation support for a protracted period (more than 8-10 days) should therefore be able to cope for at least 12 hours with moderate CPAP before extubation/decannulation is attempted. Such a conservative attitude may, however, conflict with the requirements for rapid patient turn-over in a busy ICU.

Some patients do well with a low respirator support pressure but develop respiratory distress after a few minutes of spontaneous unsupported ventilation. In such situations, it is worth considering the possibility that the tube/cannula may be partly blocked with dried mucus or blood, this may go unnoticed as long as the dimension of the still open channel continues to admit a suction catheter.

Use of weaning protocols.

To ensure that the weaning process is initiated as early as possible, many ICUs utilize protocols that define when and how weaning should start. These vary somewhat between different institutions and geographical regions, as well as with which group of ICU professionals that are responsible for implementing the protocol in each patient. In the USA and Canada, respiratory therapists and specialist nurses are often responsible for weaning trials, in most other parts of the western world, doctors and specialist nurses decide when to initiate the weaning process. A Cochrane analysis of the benefits of using weaning protocols concluded with finding an all-over 26% decrease in time before liberation from the ventilator in most patient groups, but also warned about the reliability of this conclusion due to the heterogeneity of protocols used in the various included studies (412).

Endotracheal tubes vs tracheostomies for extended ventilation support.

In most patients needing invasive mechanical ventilation, endotracheal tubes (placed under emergency or elective circumstances) represent the access to the airways. In adults today, these tubes are usually made of polyvinyl chloride plastic (PCV) equipped with inflatable, high volume, low pressure (HVLP) cuffs to ensure an air-tight seal; for an overview of the development and

descriptions of common types of endotracheal tubes, see ref (413). In the 1960-1970-ties, reusable rubber tubes were still in use also for long-term mechanical ventilation, the first-generation PCV tubes that were introduced in the late 1960-ties still had high-pressure cuffs. Due to this, older literature describing the damages caused by the long-term use of endotracheal tubes (414) does not reflect today's situation.

Nevertheless, a recent study employing direct inspection of the larynx after 0.5 to 3.5 days of intubation, found visual signs of laryngeal injury in 57% of those examined. Special risk factors for such injury were diabetes mellitus, high body mass index, and tube size greater than 7.0 (415). The choice of tube size is important, in patients who need bronchoscopy; bronchoscopes with a suction channel occlude a large part of the 7.0 tube and may create unintended very high pressures during bronchoscopy if maintaining normal ventilation volumes are attempted (334).

Laryngeal injury, as well as many other medical and practical problems associated with endotracheal tubes during prolonged mechanical ventilation, can be avoided by performing a tracheostomy and replacing the endotracheal tube with a tracheal cannula. This type of airway is better tolerated by lightly sedated or awake patients; as it reduces the need for sedation, it may also facilitate weaning and shorten the weaning period. Therefore, about 10% of the patients needing protracted mechanical ventilation (i.e. mechanical ventilation for more than 10-14 days) receive a tracheostomy (416). A prediction about the probable need for tracheostomy can often be made within the first 7-10 days of mechanical ventilation (417). Individual consideration must be given not only to the disease or trauma type but also to co-existing diseases, age, the patient's mental state, and the capacity for tolerating discomfort from the tube.

Early tracheostomy (i.e. after 3-7 days) has been advocated for patients who show little progress during the first few days of mechanical ventilation (315). Tracheostomy introduces, however, a risk of procedure-associated complications (e.g. bleeding, pneumothorax) in the acute phase as well as later complications (e.g. laryngeal stenosis, stoma infections) (418).

Whether early tracheostomy facilitates weaning may depend on which patient population is investigated. In a predominantly trauma population, no significant benefits were found (419), while a benefit on mortality as well as ICU days was found in a medical population (420). A Cochrane meta-analysis concluded that there may be a slight reduction in mortality as well as time on mechanical ventilation for patients that receive an early tracheostomy (421), another analysis found only a reduction in ventilation days but no effect on mortality or pneumonia (422). In one study, greater patient comfort was reported to be the sole benefit of early tracheostomy (423).

A meta-analysis comparison of conventional surgical tracheostomy and newer percutaneous techniques found that the latter was associated with fewer wound infections (moderate-quality evidence) and unfavorable scarring (low-quality evidence). The percutaneous technique may also have a slight beneficial effect on mortality and serious adverse effects including bleeding, the quality of evidence presented supporting this assumption has been very low (424).

A drawback of tracheostomy cannulas is that most of them cannot be clamped during procedures where the ventilator circuit needs to be disconnected from the airways. For most patients, a recruitment maneuver immediately after disconnection can remedy the sudden worsening of gas exchange often seen in "PEEP-dependent" patients after the loss of positive airway pressure for only a few seconds. For a few patients, however, a protracted period of hypoxemia may ensue before the oxygenation is stabilized anew. By following the procedures for short term disconnec-

tion outlined above, the risk of hypoxemia can be reduced but not abolished. The effect of applying an inspiratory hold on the circulation of normo- or hypovolemic patients during such procedures should, however, not be underestimated.

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PART 5. ACID-BASE BALANCE, ANALYSIS OF BLOOD GASES

5-1. GENERAL ASPECTS OF ACIDS AND BASES
5-2. ACID-BASE BALANCE IN THE HUMAN ORGANISM
5-3. DISTURBANCES IN THE ACID-BASE EQUILIBRIUM
5-4. INTERPRETATION OF LABORATORY RESULTS; DIAGNOSIS OF ACID-BASE DERANGEMENTS AND TREATMENT OPTIONS

INTRODUCTION.

Optimal function of the human organism requires a stable concentration of free H^+ ions ($[H^+]$) in the body fluids surrounding enzymes and other proteins. Normal cellular metabolism generates acid metabolites continuously, these are transported out of the cells and away from the tissues by the blood after diffusing through the interstitial fluid. Free H^+ ions do not pass directly through cell membranes; they can, however, be transported by ion exchanger proteins embedded in the membranes (1, 2) to preserve the intracellular $[H^+]$ within the survivable range (3). Important extracellular cascade systems like the coagulation system also function best when the $[H^+]$ level in the blood is close to the normal range (4).

Any condition or disease that creates an *imbalance* between the *generation* and *elimination* of metabolites with acid or base properties, or introduce *exogenous* agents with such properties into the organism, induce a deviation from the normal $[H^+]$ in the body fluids. Both *increased* and *decreased levels* of $[H^+]$ may exert negative effects on the amount of O_2 available to the tissues, through their effects on

- **The heart and the circulation,** as increased $[H^+]$ decrease myocardial contractility as well as vascular reactivity and thus affects both the total blood flow and its distribution (Part 5-4) *and*
- **The O_2 binding to the hemoglobin molecule,** as changes in $[H^+]$ alters the arterial SO_2 at a given PO_2. The importance of changes in the HbO_2 may be modest at normal- and supernormal PO_2 levels but increases as the PO_2 decreases and in extreme acidosis and alkalosis (Part 2-3, the HbO_2 dissociation curve).

In most cells, the normal intracellular $[H^+]$ is in the 50-100 nmol/l range, corresponding to a pH value of 7.00–7.30 (for relationship between $[H^+]$ and pH, see fig. 5-1). This $[H^+]$ is slightly higher than that in the interstitial fluid and normal venous blood (44 nmol/l *or* pH 7.36); the normal arterial $[H^+]$ is approximately 40 nmol/l, equivalent to pH 7.40. An $[H^+]$ gradient thus exist between intracellular fluid, the interstitium and arterial blood.

In clinical medicine, deviations from the normal acid-base state in the organism are traditionally measured as **$[H^+]$** changes in **arterial blood** and presented as **pH** values (see below). The *quantitative* aspects of acid-base balance in arterial blood differ between the conditions in intracellular fluid, interstitial fluid, and venous blood. Most of the clinically important *qualitative* changes are, however, reflected by the changes in the arterial blood (or sometimes even better in mixed venous blood). Arterial blood samples are relatively easy to obtain; changes in their $[H^+]$, regardless of etiology, are traditionally classified as

- **Acidosis,** if the **$[H^+]$** is increased **above 45 nmol/l (pH ≤ 7.35),** *or*
- **Alkalosis,** if the **$[H^+]$** is decreased **below 35 nmol/l (pH ≥ 7.45).**

Both acidosis and alkalosis are further subdivided into **respiratory** (where the *primary* cause of changes in $[H^+]$ is an alteration of blood CO_2 levels), *or* **metabolic** (where the *primary* cause of $[H^+]$ changes is due to other causes, but where *secondary* alterations in CO_2 usually accompanies the initial $[H^+]$ changes), *or* **combined** respiratory-metabolic disturbances.

In addition to $[H^+]$, blood gas analyzers also measure the pressure of O_2 and CO_2 dissolved in the blood. These pressures are not always representative for the *total content* of these two gases in the blood; especially for O_2, the O_2 content relative to a given PO_2 may vary with 50% or more when the HbO_2 affinity changes (fig 4-12, fig 2-21) or carbon monoxide (CO) is present (fig 2-22). Many modern analyzers therefore also measure the HbO_2 saturation, as well as the CO content of the blood, directly.

In some groups of patients, especially those in circulatory failure and shock, serial analysis of acid-base balance, as well as the O_2 and CO_2 content of the blood draining the tissues (i.e. the venous blood, where the mixed venous blood is representative for the whole organism), may contribute additional information about both the severity of the condition as well as the effect of therapeutic interventions.

The organism has three lines of defense against changes in $[H^+]$:

i) **Buffering.** The **buffers** (see Buffer systems below) are intra- and extracellular molecules (mostly proteins and weak acids) that can bind or release free H^+ ions almost instantaneously in response to changes in $[H^+]$. This keeps the $[H^+]$, both intracellularly and in the arterial blood, within survivable limits.

ii) **Adjusting the ventilation pattern** and thus the CO_2 excretion to keep the arterial CO_2 concentration at levels that minimize $[H^+]$ changes, *and*

iii) **Modifying the function of renal tubuli cells** to excrete more H^+ by the urine, or retain more H^+ in the blood, as needed to re-establish a normal acid-base balance.

Understanding the various mechanisms leading to acidosis and alkalosis, as well as the compensatory responses mounted by the organism, requires some understanding of normal and abnormal metabolism, as well as general chemistry, biochemistry, and physiology. Some of the more important aspects are outlined in Part 2, the Appendix, and the following sections of Part 5. **Acute acidosis** is the most common acid-base disturbance associated with severe disease in acute and emergency medicine, as well as during anesthesia and in intensive care. The primary focus in this compendium is therefore on this type of derangement.

5-1. GENERAL ASPECTS OF ACIDS AND BASES

PROPERTIES OF ACIDS, BASES, AND SALTS

Acids. In human physiology and biochemistry, the most common definition of an acid is **a** substance that can **donate** (*or liberate*) **free hydrogen (H^+) ions** (protons) when dissolved in an aquatic solution. This definition was initially proposed by Arrhenius (5) and later expanded by Brønstedt and Lowry (6). An alternative, and more general definition of acids suggested by Lewis (7) states that *any substance that can accept a pair of electrons is an acid.* Substances that fulfill this latter definition but not the former are sometimes called "Lewis Acids". In medicine, the Brønstedt and Lowry concept remains the most common, the Lewis definition is mostly used within the field of chemistry. Although not perfect for explaining all types of acid-base disturbances, the Brønstedt and Lowry definition is relatively easy to understand and is the one used in this compendium.

Bases. A *base* dissolved in an aquatic medium was originally defined by Arrhenius as a **hydroxyl (OH^-) ion** (also called hydroxide ion); Brønstedt and Lowry expanded the definition of a base to be any substance that could **accept a free H^+ ion** (and thus create OH^- ions by stripping H^+ ions from water molecules when added to aquatic media). The Lewis definition of a base was *any substance that could donate a pair of electrons.* For those interested in the historical development of the acid-base concept, several reviews (refs. 8, 9, 10) can be recommended.

Salts. Salts are compounds formed by a reaction between acids and bases. Many salts (e.g. NaCl, which can be formed by a reaction between the acid HCl and the base NaOH) dissolve easily in water and other aquatic media; NaCl dissociates into a **cation** (**Na^+**) with a **net positive charge** and an **anion** (**Cl^-**) with a **net negative charge**. Depending on the type of acid and base involved in the reaction creating the salt, dissociation of some types of salt in aquatic media may lead to a hydrolysis reaction with the production of *either* increased H^+ ions *or* OH^- ions, making the solution more acid (acid salts) or alkalotic (basic salts), respectively, after the salt has dissociated.

Salts like NaCl dissociate with only a modest effect on the concentration of H^+ or OH^- in the medium (neutral salts), a commercial NaCl 0.9% solution for infusion ("isotonic saline") has a pH of about 5.5-5.6; most of the increased acidity compared to pure water is due to dissolved CO_2, the packaging material and sterilization process (11). The addition of substantial amounts of NaCl to the body fluids of an intact organism (by *infusion* or *ingestion*) may, however, change the concentration of other constituents of the fluid (e.g. buffers, see below) and stimulate cell membrane ion exchange mechanisms whose task is to keep the Cl^- concentration in extracellular fluid at about 70% of the Na^+. The result of increased Cl^- concentrations relative to Na^+ (i.e. a decreased $[Na^+]$ - $[Cl^-]$ difference) may be an increased dissociation of water (see below) and the development of acidosis (Part 5-3, see also the Stewart principle).

Properties of acids and their conjugate bases.

According to the Brønsted/Lowry definition, any acid (usually written as **HA**) consists of at least one **H^+** ion chemically bound to another molecule with one or more negative charges, an *anion* (**A^-**). The anion can be a single charged atom (as Cl^- in hydrochloric acid, HCl), or a molecule consisting of several atoms (as bicarbonate, HCO_3^-, in carbonic acid, H_2CO_3) or even large molecules capable of binding a substantial amount of H^+ ions (proteins like hemoglobin and albumin, see below). All anions capable of binding one or more H^+ ions are by definition bases, the **A^-** ion

(i.e. the part of an acid remaining *after* the release of H^+ ions in aquatic media) is therefore called the **conjugate base** of the acid. The free H^+ ions (see below) released are nonspecific and common for all acids; the properties of each acid is determined by the chemical characteristics exhibited by their conjugate base. In clinical medicine, an increased *concentration of the acid's conjugate base* (e.g. lactacidosis, ketoacidosis) identifies the metabolic disturbance responsible for the acidosis.

Free H^+ ions do not really exist in an aqueous solution. At the instant when the acid molecule dissociates and the chemical bond between H^+ ions and the conjugate base is broken, the liberated H^+ ion bonds with a water molecule, H_2O, to create **H_3O^+ ions** (called hydronium *or* hydroxonium ions). The correct equation describing the dissociation of an acid in an aquatic solution is therefore

$H_2O + HA \rightarrow H_3O^+ + A^-$

In aquatic solutions, water molecules are abundant. The amount of H_2O molecules, with a molecular weight of 18 daltons, in pure water is about 55.5 mol/l (see Apx), far above the number of molecules of acid present in biological systems. The number of **H_2O** molecules is therefore never a limiting factor in such reactions, which is why H_2O often is omitted from the equation above. In most of the medical literature, including this compendium, the H_3O^+ ions are, for simplicity, labeled as H^+. The reaction representing the dissociation of any acid in an aquatic solution is therefore usually written as

$HA \rightarrow H^+ + A^-$

with the understanding that "free **H^+**" stands for **H_3O^+** *and* that **H_2O** molecules are abundant.

When reaction factors are presented within square brackets (i.e. **$[H_2O] + [HA] \leftrightarrow [H^+] + [A^-]$**), their concentration (usually measured in mol/l or fractions of a mol per liter, Apx) is implied. The concentration of most acids (in reality, their conjugate bases) in body fluids is in the 0.1-50 mmol/l range. Due to the effects of various chemical systems for neutralizing $[H^+]$ in the fluids of the human body (buffers, see below), the mean **$[H^+]$** in normal arterial blood is between 2 500 and 1 000 000 times lower than the concentration of the conjugate bases.

The law of mass action: reversible reactions in water and body fluids.

The law of mass action describes the behavior of substances involved in reversible chemical reactions**.** After the initial dissociation of an acid or a base in an aquatic fluid, the concentration of the elements involved (**HA, H^+,** and **A^-** *or* **B, BH,** and **OH^-**) rapidly reaches equilibrium. The law of mass action states that *a change in the concentration of one of the elements in the reaction results in changes in the concentration of the other elements until a new equilibrium between the elements is established.*

The H^+ ion concentration expressed as a pH value.

As the **$[H^+]$** in human intra- and extracellular fluid is very low, their concentration is, by convention, usually reported as pH units. The pH is the positive value of the logarithm (with 10 as a base) of the *molar concentration* of free H^+ ions, as suggested by Sørensen (12). The **$[H^+]$** in normal arterial blood is 40 nmol/l (i.e. 0.000 000 040 mol/l), the corresponding value in logarithmic notation (see also Apx) is $10^{-7.40}$ mol/l, giving a pH value of 7.40 (see fig. 5-1).

Dissociation of acids in pure water and the dissociation constant.

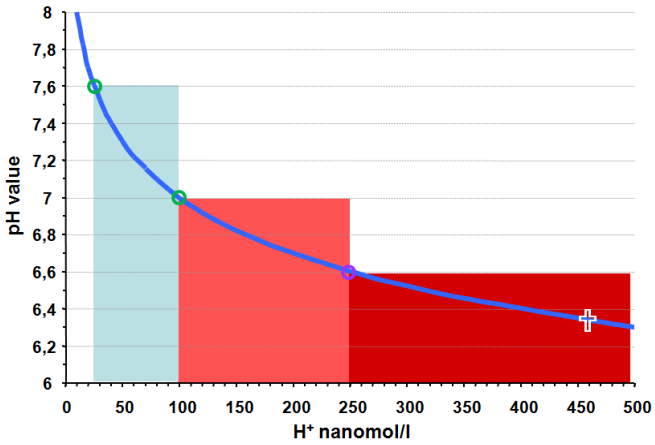


Figure 5-1. *Curve showing the relationship between the free H⁺ concentration (X axis) and the corresponding pH value (Y axis). The part of the curve within light blue area denotes H⁺ concentrations in human arterial blood that are well tolerated by otherwise healthy persons. Levels within the light red area may be associated with serious disease, those within the dark red are usually associated with life threatening conditions in connection with trauma, shock or severe disease. The cross marks the limit for reported survival (see Part 5-3).*

After adding an acid to water, an equilibrium between the relative concentration of the **non-dissociated acid** [**HA**] and the **dissociation products** [**H⁺**] *and* [**A⁻**] is rapidly reached. In *pure water*, the increase in [**H⁺**] and [**A⁻**] resulting from the dissociation must be equal. This equilibrium, and thus the relative concentrations of **HA**, **H⁺**, and **A⁻** at equilibrium, differ substantially between various acids (see *weak* and *strong* acids below); the chemical properties of the *conjugate base* **A** determine the strength of the **HA** binding, and thus the degree of dissociation when acids dissolve in water. The dissociation level at equilibrium is defined by the *dissociation constant* (**K_a**) for the acid. It is calculated as the product of the dissociated [**H⁺**] and [**A⁻**] molecules, divided by the remaining non-dissociated acid [**HA**], and is written as:

$$K_a = \frac{[H^+] \times [A^-]}{[HA]}$$

The Ka value changes with both temperature and the concentration of various electrolytes (e.g. the salinity) in the solute. If a theoretical acid **X (HA$_X$)** is 99.99% *dissociated* into **H⁺** and **A$_x^-$**, (i.e. a *fraction* of 0.9999 of the acid molecules dissociates when **HA$_X$** is added to water), 0.01% (a *fraction* of 0.0001) *remains non-dissociated as* **HA$_X$.** The **K_{ax}**, when expressed as fractions of the initial number of HA molecules dissolved in water, then becomes

$$K_{ax} > \frac{0.9999 \times 0.9999}{0.0001} = 9998,$$

i.e. 0.9998 x 10^4 *or close to* 1x10^4.

If, on the other hand, another theoretical acid, the weak acid **Y (HA$_Y$)** are 1.0 % (a *fraction* of 0.01) *dissociated* into **H⁺** and **A$_Y^-$**, 99.0% (a *fraction* of 0.99) *remains non-dissociated as* **HA$_Y$**. Calculation of **K_{ay}**, using fractions as above, becomes

$$K_{ay} > \frac{0.01 \times 0.01}{0.99} = 0.00010,$$ i.e. 1.0101 x 10^{-4} *or close to* 1x10^{-4}.

If 27% of the acid **Z** is *dissociated*, and the remaining 73% is *non-dissociated,* the equation becomes

$$K_{az} = \frac{0.27 \times 0.27}{0.73} = 0.0998,$$ i.e. 0.998 x 10^{-1} *or close to* 1x$10^{-1.0}$, a value often used as a border between strong and weak acids, *see below*.

For a theoretic acid to have a **K_a** of 1, it must be between 61.8% and 61.9% dissociated. See also table 5-1 for more calculation examples.

Dissociation constants expressed as the pK_a value.

The dissociation constant **K_a** of acids is often expressed as the **pK_a** value, which is defined as the *negative logarithm (with base 10) of the* ***K_a*** (analogous to **pH** as the negative logarithm of the **$[H^+]$**, see above); i.e. **$pK_a = -\log_{10}$** of **K_a**. If K_{ax} is set to 10^4 in the example above for **HA_X**, the pK_a becomes -4, for **HA_Y**, if the K_{ay} is $10^{-1.0}$, the pK_a becomes 1. Other examples of such calculations for the dissociation of various theoretical acids, in addition to those for lactic acid and carbonic acid, are presented in table 5-1.

Definitions of weak and strong acids.

pKa	Ka	$[H^+]$	$[A^-]$	[HA]	$[A^-]/[HA]$
-5,00	99998,000010	0,99999	0,99999	0,00001	**99999,0**
-4,00	9998,0001000	0,99990	0,99990	0,00010	**9999,00**
-3,00	998,00100000	0,99900	0,99900	0,00100	**999,000**
-1,99	98,010000000	0,99000	0,99000	0,01000	**99,0000**
-0,91	8,1000000000	0,90000	0,90000	0,10000	**9,00000**
0,30	0,5000000000	0,50000	0,50000	0,50000	**1,00000**
1,00	0,09986	0,27000	0,27000	0,73000	**0,36986**
1,95	0,0111111111	0,10000	0,10000	0,90000	**0,11111**
3,85	0,0001411430	0,01181	0,01181	0,98819	**0,01195**
4,00	0,0001010101	0,01000	0,01000	0,99000	**0,01010**
6,00	0,0000010010	0,00100	0,00100	0,99900	**0,00100**
6,10	0,0000007928	0,00089	0,00089	0,99911	**0,00089**
6,60	0,0000002501	0,00050	0,00050	0,99950	**0,00050**
8,00	0,0000000100	0,00010	0,00010	0,99990	**0,00010**
10,00	0,0000000001	0,00001	0,00001	0,99999	**0,00001**

Concentrations of $[H^+]$, $[A^-]$ and [HA] in fractions of a mole.
Equations: 1: **Ka** = ($[H^+]$ x $[A^-]$) / [HA] . 2: **pKa** = - ($\log_{10}$ of Ka).

Table 5-1: Calculated values of Ka and pK_a *corresponding to different degrees of dissociation of theoretical acids in pure water. The ratios between conjugate base and non-dissociated acid,* **($[A^-]$/ [HA]),** *are also shown. Approximate values for lactic acid-lactate (light lilac) and carbonic acid-bicarbonate ratios (light blue), based on their pK_a of 3.85 and 6.1, respectively, are included. Dissociation of a theoretical acid with pKa=1 (the arbitrary border between weak and strong acids) is marked in light green. The pKa shown are approximate values.*

Acids are often divided into strong and weak acids according to the degree of dissociation in water. There is no universally accepted definition of where the boundaries for the degree of dissociation should be set. The higher the K_a, the stronger the acid. A simple distinction, classifying all acids with a $K_a > 0.1$ (i.e. > 27% of the acid is dissociated when added to water, see above and table 5-1) as strong acids, and those with a $K_a < 0.1$ as weak, is often used. The really strong acids (i.e. those fully dissociated in water) are few; most acids are classified as weak but vary in their dissociation with several magnitudes.

The **strength** of an acid is a chemical term that defines its **dissociation** when dissolved in pure water. This must not be confused with the *concentration* or *dilution* of an acid. Neither can the terms *strength* and *corrosive/destructive* properties be used interchangeably, as these properties are not necessarily related. An example of this is Hydrofluoric acid (**HF**) which, in terms of dissociation, is a *weak acid* with a K_a of 7.2×10^{-4}, but is extremely *corrosive* and *destructive* to most materials and human tissue.

The dissociation of strong acids is irreversible.

Strong acids dissociate almost completely when dissolved in pure water (table 5-1); calculation of the K_a has little meaning. For a strong acid like hydrochloric acid (HCl), virtually all of the acid (more than 99.9999%) is dissociated at equilibrium; the K_a is then *above* 1 000 000 or 10^6. The dissociation reaction for a strong acid can for all practical purposes be written as a one-way reaction,

HA ➡ H^+ + A^-.

The dissociation of weak acids is reversible.

Only a minor part (often less than 1%) of the acid molecules dissociate when a **weak acid** is dissolved in pure water; i.e. a substantial part of the acid (**HA**) is still non-dissociated when the reaction reaches equilibrium (Table 5-1). The dissociation reaction is *reversible* and follows the law of mass action, with the equation written as

HA ⇔ H^+ + A^-.

The most *central conjugate base* of a weak acid in human acid-base physiology is **bicarbonate**, **HCO_3^-** (the conjugate base of carbonic acid, **H_2CO_3**, see below). A second conjugate base of importance in medicine is **lactate**, **$C_3H_5O_3^-$** (the conjugate base of lactic acid, **$C_3H_6O_3$**).

The above equilibrium, with implies an *equal* increase in concentrations of free **H^+** and **A^-** at equilibrium, is valid only for *pure water*. If the dissolving medium contains molecules that can bind most of the H^+ ions liberated by the dissociation and thus remove them from the solution, the final concentrations of free [**H^+**] and [**A^-**] in the solution at equilibrium may be *very* different (fig 5-2). In most body fluid, the various buffers have such properties.

In the human organism, most fluid compartments (especially the blood) contain buffers with a large capacity for binding the H^+ ions liberated by dissociation of acids. The reaction above then continues to the right until a new equilibrium is reached; the [**A^-**] is then greatly increased relative to free [**H^+**]. Lactic acid is so highly dissociated at H^+ concentrations compatible with survival (fig. 5-1) that it dissociates like a much stronger acid with a concentration of [**A^-**] (lactate) more than 3 500 times higher than the [**HA**] (lactic acid) at equilibrium.

Dissociation of bases.

When a base (B) is dissolved in aquatic media, it strips H^+ ions from water molecules, which then become **reactive hydroxyl ions**, **(OH^-)**. The dissociation reaction is written

$B + H_2O \rightarrow BH + OH^-$

Most of the OH^- ions will bond with some of the free H^+ ions (i.e. **H_3O^+**, which are always present in an aquatic solution - see above), this creates more **H_2O** and reduces the concentration of free H^+ ions.

Analogous to the terminology for acids, the **B** in the BH compound is called the **conjugate acid of the base**; also bases may be classified as weak or strong. With the ingestion of a normal western diet, the net production of acids by the human metabolism exceeds the production of bases. A reduced H^+ concentration in body fluids (alkalosis) is therefore most often (but not always, see below) a result of *either* an increased excretion of CO_2 *or* pathological losses of H^+ from the gastrointestinal system or the kidneys.

Spontaneous dissociation of water and its content of H^+ ions.

In pure water, a very small number of the H_2O molecules dissociate spontaneously into H^+ and OH^- ions. Any aqueous solution therefore always contains small amounts of free H^+ ions (in reality H_3O^+ ions, see above), as well as OH^- ions. Water can therefore act as an acid as well as a base; the degree of dissociation, and thus the amount of free H^+ ions and the acidity of pure water, increases with water temperature. At **0°C**, water has a [H^+] of **34 nmol/l** (pH 7.47), at **25°C**, the [H^+] is **100 nmol/l** (pH 7.00) and at **37°C**, the [H^+] is **160 nmol/l** (pH 6.80). By convention, a *neutral pH* is defined as *pH of 7.00*. Even if the body fluids consist mainly of water,

their content of various weak acids and proteins that bind H^+ ions (see buffers below) results in a different concentrations of free H^+ in body fluids than those in *pure water*. In arterial blood at 37°C, the normal pH (i.e. 7.40, an $[H^+]$ of 40 nmol/l) is slightly alkaline relative to pure water.

According to the Stewart principle, the balance between the strong (i.e. fully dissociated) cations and anions in an aquatic medium also affects the dissociation of water (see dissociation of salts above). If the $[Cl^-]$ *decreases* more than $[Na^+]$, the *difference* between the major extracellular ions $[Na^+]$ and $[Cl^-]$ increases. The dissociation, and thus the $[H^+]$ in body fluids is then reduced, leading to "hypochloremic" alkalosis. If the $[Cl^-]$ *increases and* the $([Na^+]- [Cl^-])$ difference decreases, increased dissociation leads to "hyperchloremic" acidosis.

WEAK ACIDS ARE IMPORTANT BUFFERS IN BODY FLUIDS

A **weak acid** that is partly dissociated at the actual pH of the solvent can act as an **H^+ acceptor** when the **$[H^+]$** in the solution increases (resulting in *decreased dissociation* and *increased concentration* of the **HA**) **or an H^+ donor** (resulting in *increased dissociation* and *reduced concentration* of **HA**) when it diminishes. Weak acids and protein molecules with such properties act as **buffers**; within a certain **$[H^+]$** range, specific for each buffer, it can keep the free **$[H^+]$** in the solution within narrow limits when other acids or bases are added.

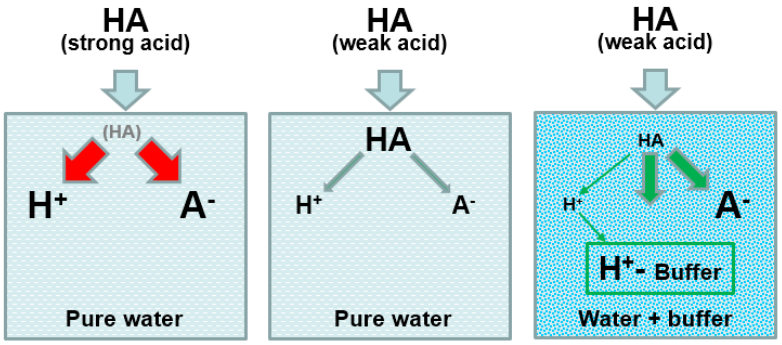
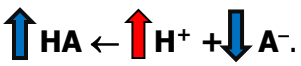


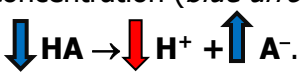
Figure 5-2. *From left: Dissociation of a strong acid, of a weak acid, and of the same weak acid when efficient buffers are present. The concentration of the conjugate base A^- of a weak acid, relative to HA, increase considerably when a weak acid (suitable as a buffer, see below) is also present.*

In the human organism, the main purpose of such buffer systems is to keep the **$[H^+]$** in the body fluids within acceptable limits in all fluid compartments, primarily the intracellular ones (fig 5-2).

A primary increase in **$[H^+]$** due to increased levels of metabolic or exogenous acids (*red arrow* below) causes more **H^+** ions to be bound by the conjugate base **A^-** of the weak buffer acid; the equation runs to the left with a decrease in the conjugate base **A^-** and an increase in **HA** concentrations (*blue arrows)* which limits the **$[H^+]$** increase.



Vice versa, if the **$[H^+]$** is reduced (i.e. lost from the body or bound by an excess of other A^- ions - *red arrow* below), the equation runs to the right with an increase in **A^-** and a decrease in **HA** concentration (*blue arrows*), again limiting the change in **$[H^+]$**.

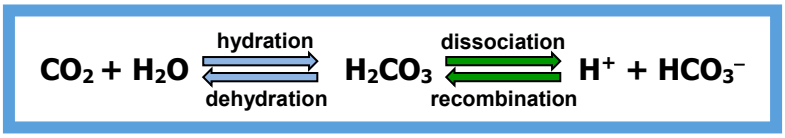


Thus, the presence of weak acids that function as effective buffers at the normal **$[H^+]$** range in the human organism can avert large shifts in **$[H^+]$.** The most effective buffer is a compound where the **ratio** between **A^-** and **HA** is close to **1:1** at the **normal pH** of a solution *before* the addition or removal of **H^+** ions.

In the human organism, the **phosphate buffer system** where $H_2PO_4^-$ (derived from the weak acid *phosphoric acid*, H_3PO_4) and its conjugate base HPO_4^{2-}, is an important intracellular buffer. In the extracellular space, *carbonic acid* (H_2CO_3) and its conjugate base **bicarbonate** (HCO_3^-) is the major buffer. The amino acid side chains of **hemoglobin,** as well as **albumin,** have a **surplus of negative charges** which give them important buffer properties (see Part 5-2 for details) in blood and extracellular fluid.

Mass action effects involving CO_2 reactions in pure water.

A central example of mass action in biochemistry is the *reversible* two-step conversion of the gas CO_2 to H^+ and bicarbonate (HCO_3^-). When CO_2 gas dissolves in pure water, some of the molecules (less than 1% at body temperature) react with water molecules (are *hydrated, step 1, blue arrows below*) and form the weak acid *carbonic acid* (H_2CO_3). The hydration (or dehydration) reaction is slow (seconds or parts of a second). The formed *carbonic acid* molecules rapidly dissociates (s*tep 2, green arrows below*) into equal amounts of *H*$^+$ and *bicarbonate* ions:



Mass action effects involving CO_2 reactions in the blood.

Most of the **CO_2** hydration/dehydration and **H_2CO_3** dissociation/recombination in the human organism occurs *inside the erythrocytes*, where conditions are very different from those in pure water.

i) **The speed of hydration.** Inside the erythrocytes, the enzyme *carbonic anhydrase* (**CA**), catalyzes the hydration reaction and increase its speed 10 000 – 30 000 times. This enzyme is mainly found inside erythrocytes and renal tubuli cells, and also on some endothelial surfaces. In the presence of this enzyme, the hydration (and also the dehydration) reaction becomes virtually instantaneous (milliseconds or parts of a millisecond).

ii) **The removal of the free H^+.** Almost all the H^+ ions resulting from the **H_2CO_3** dissociation *inside* the erythrocytes are bound (buffered) by the Hb molecules; the increase in *free* **H^+** when more CO_2 is dissolved in the blood during passage through the microcirculation is therefore minuscule compared to that of **HCO_3^-** (i.e. nanomoles vs millimoles, see Law of mass action above). Due to the effect of CA and Hb buffering of H^+, a final equilibrium between CO_2, HCO_3^- and H^+ in the blood is not reached until about 90% of the CO_2 molecules in the blood have been hydrated (see also fig. 5-3).

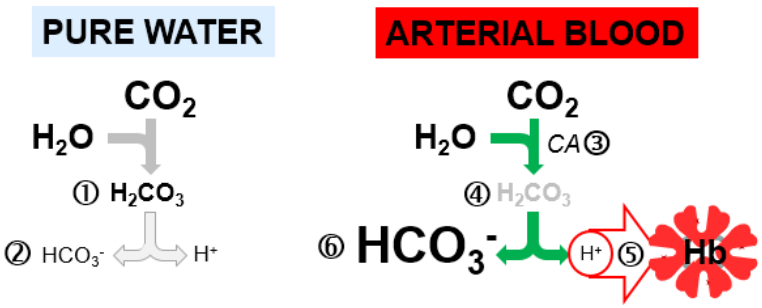
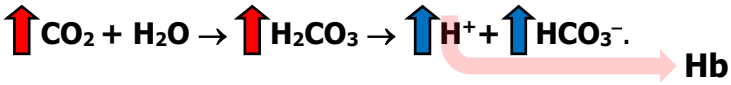


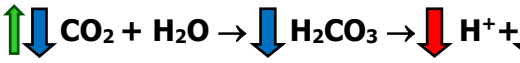
Figure 5-3. *Hydration of CO_2 in water (left) and blood (right). Reaction between CO_2 and H_2O ① in water is slow and less than 1% of the CO_2 reacts with H_2O to generate H_2CO_3 which then dissociate ② into HCO_3^- and H^+. When CO_2 enters the erythrocytes, the enzyme carbonic anhydrase (CA) ③ catalyze the reaction between CO_2 and H_2O, which then become almost instantaneous. The H_2CO_3 ④ dissociate immediately; as the H^+ are buffered by Hb molecules ⑤; the dissociation reaction continues until about 90% of the CO_2 molecules are converted to HCO_3^- ⑥.*

As more CO_2 is generated continuously by the tissue metabolism and added to the blood passing through the tissue

microcirculation, the **concentration of dissolved CO_2 molecules** (measured as PCO_2) **increases** and more **H_2CO_3** is generated (*red arrows* below). Almost all the **H_2CO_3** subsequently dissociate and the reaction proceeds to the right, leading to a secondary increase in the concentration of both **H^+** and **HCO_3^-** (*blue arrows*). Most of the **H^+** ions produced by this reaction are bound by the hemoglobin molecules (*pink arrow*) and thus removed from the erythrocyte intracellular fluid (see above). The reaction then proceeds further to the right. At equilibrium, the final change in the blood [**H^+**] (i.e. in the pH) is minuscule compared to that of **HCO_3^-**.



A **primary reduction** of the concentration of either **H^+** (alkalosis) *or* **HCO_3^-** *or* both (*red arrows*,) also shifts the equation to the right, which decreases the **H_2CO_3** concentration (*blue arrow*), followed by a decreased PCO_2 as a secondary effect. In the human organism, such a decrease of CO_2 is not found, as reduced **[H^+]** also decrease ventilation and CO_2 excretion *in excess* of the reduced CO_2 generation, and an *increased* PCO_2 (*green arrow*) is usually seen



If, on the other hand, concentrations of either **H^+** (acidosis) *or* **HCO_3^-** increase (**H^+** increase as a result of increased production of other acids, **HCO_3^-** after the addition of base as **$NaHCO_3^-$**, respectively, *red arrows* below), the reaction shifts to the left, increasing the concentration of **H_2CO_3** and its dehydration to CO_2 gas (*blue arrows*). As increased **[H^+]** in the arterial blood stimulates ventilation and CO_2 excretion *in excess* of the increased CO_2 generation, a *reduced* PCO_2 (green arrow) is usually found in clinical medicine

A primary PCO_2 decrease also reduces the **H_2CO_3** concentration (*red arrows*), shifting the reaction to the left and reducing both **H^+** and **HCO_3^-** (*blue arrows*), (see also Part 5-2).

The presence of buffers in the body fluids, as well as the respiratory and renal adaptions to changes in $[H^+]$, ensures that the final changes in $[H^+]$ are minuscule compared to the changes in HCO_3^- (see also Part 5-2 and Part 5-3).

Dissociation of acids: K_a, [H^+] and buffers.

The equation defining the dissociation constant K_a for any acid **(HA)** in *pure water* (see above), can also be written as

$$K_a = [H^+] \times \frac{[A^-]}{[HA]}$$

As the K_a of a given acid is a constant, any increase in free **[H^+]** (e.g. addition of another acid, *red arrow* below) must lead to a proportional reduction of the ratio between the conjugate base **[A^-]** and non-dissociated acid **[HA]** (*blue arrow*) of a buffer.

$$K_a = \uparrow [H^+] \times \downarrow \frac{[A^-]}{[HA]}$$

How the buffer dissociation changes with [H^+]: calculation examples.

If the free **[H^+]** increases from 40 nmol/l (pH 7.40) to 100 nmol/l (pH 7.00), the **[H^+]** increases by a factor of x 2.5 (a *fraction* of 2.5 of normal (**green**)). For the K_a to remain constant, the

[A⁻]/ [HA] ratio must then be reduced by the inverse factor, i.e. the normal ratio multiplied by 1/2.5, reducing the ratio to 40% of the previous value:

$$\mathbf{K_a} = (\mathbf{2.5} \times [\mathbf{H^+}]) \times \left(\frac{\mathbf{1}}{\mathbf{2.5}} \times \frac{[\mathbf{A^-}]}{[\mathbf{HA}]}\right)$$

Using the concentrations of the conjugate base bicarbonate (**A⁻** = **HCO_3^-**) and carbonic acid (**HA** = **H_2CO_3,** which is proportional to the **PCO_2,** see below) as an example, this means that the **[HCO_3^-]**, relative to **H_2CO_3** (*or* to **PCO_2**) is reduced to 40% of normal at pH 7.00.

A reduction in the **[H^+]** by 50% (to 20 nmol/l *or* pH 7.70) would require that the **[HCO_3^-]**, relative to [**H_2CO_3**] (*or* to **PCO_2**), becomes twice as high as normal:

$$\mathbf{K_a} = \left(\frac{\mathbf{1}}{\mathbf{2}} \times [\mathbf{H^+}]\right) \times \left(\mathbf{2} \times \frac{[\mathbf{A^-}]}{[\mathbf{HA}]}\right)$$

In the intact organism, adjustments of ventilation and renal function reduce the initial change in **[H^+]**; when this occurs, the **[HCO_3^-]/[H_2CO_3]** ratio also change when a new equilibrium is reached.

The Henderson-Hasselbalch equation.

If all variables in the equation for calculating **K_a** are expressed as logarithms of the base 10, the equation becomes

$$\log_{10} \mathbf{K}_a = \log_{10} [\mathbf{H^+}] + \log_{10} \frac{[\mathbf{A^-}]}{[\mathbf{HA}]} \quad or \quad -p\mathbf{K}_a = -\mathbf{pH} + \log_{10} \frac{[\mathbf{A^-}]}{[\mathbf{HA}]}$$

Rearranging the equation above gives

$$\mathbf{pH} = \mathbf{pK}_a + \log_{10} \frac{[\mathbf{A^-}]}{[\mathbf{HA}]}$$

This equation is known as the *Henderson-Hasselbalch equation* (13, 14). The antilog of log **([A^-]/[HA])** is the *ratio* between the concentration of the acid's conjugate base and the non-dissociated acid. If pK_a = pH, the log **[A^-]/[HA]** is 0, i.e. the **[A^-]/[HA]** ratio = 1.

When the *pH of the blood* and *pK_a of the acid* is known, the ratio between the concentration of the conjugate base A^- and the non-dissociated acid HA (e.g. between bicarbonate ions, HCO_3^-, and carbonic acid, H_2CO_3 *or* between lactate ion and lactic acid) at any pH value can be calculated. For the strong acid HCl, the pK_a is ≈ -8, and for the weak acid H_2CO_3, the pK_a at body temperature is 6.1. If the blood pH is 7.10, the log **[A^-]/[HA]** is 1, i.e. the **[A^-]/[HA]** ratio = 10.

The dissociation of carbonic and lactic acids at various pH values is shown in table 5-2; note that the concentration of bicarbonate, relative to carbonic acid (which is in equilibrium with the PCO_2, see below), is reduced from 20 to 5 if the pH is reduced from 7.40 to 6.80, (i.e. the [H^+] increases from 40 to 160 nmol) *and* the PCO_2 remains normal.

The relation between H_2CO_3, PCO_2, and bicarbonate in the blood.

After the hydration of **CO_2** to **H_2CO_3** inside the erythrocytes, the hydration and dissociation products are at all times in equilibrium with the number of CO_2 molecules dissolved as gas and measured as PCO_2. The speed of this dissociation makes the concentration of hydrated CO_2 (i.e. the [H_2CO_3]) very small; the ratio of [H_2CO_3] molecules *vs* dissolved [CO_2] has been estimated to close to 1/700 (15). The concentration of **H_2CO_3** *per se* in the blood is thus minuscule and cannot be measured routinely.

The *combined* amounts of CO_2 present as H_2CO_3 *and* as dissolved CO_2 molecules, measured in mmol/l, can be assumed to be *proportional* to the PCO_2 measured in the fluid. In equations involving H_2CO_3 in the blood**,** the sum of dissolved CO_2 and non-dissociated H_2CO_3 is, for practical reasons, lumped together as H_2CO_3. In the dissociation equation for carbonic acid, the term $[H_2CO_3]$ may, therefore, be substituted by the *measured* PCO_2 multiplied with a constant **k**:

$[H_2CO_3] = PCO_2 \times k$

When this expression is substituted for **$[H_2CO_3]$,** the equation can be written as

$$K_a = \frac{[H^+] \times [HCO_3^-]}{[PCO_2 \times k]} \quad or = \quad [H^+] \times \frac{[HCO_3^-]}{[PCO_2 \times k]}$$

where the **k** = **0.23025** mmol/kPa *or*, if PCO_2 is given in *mmHg*, **0.0307** mmol/mmHg. If normal arterial values of PCO_2 are converted, we get 5.3 kPa x 0.23025 mmol/kPa = **1.22 mmol.** If the equation above is rearranged and solved for HCO_3^-, it becomes:

$$[HCO_3^-] = (K_a \times k) \times \frac{PCO_2}{[H^+]}$$

If **$PCO_2 \times k$** is substituted for **H_2CO_3** in the Henderson-Hasselbalch equation, it can be written as

$$pH = pK_a + \log_{10} \frac{[HCO_3^-]}{[k \times PCO_2]}$$

In human acid-base balance, acute changes in blood PCO are always accompanied by a change in $[H^+]$. An acute 100% increase in PCO_2, from 5.3 to 10.6 kPa, represents an (improper) fraction of 2.0 of the normal value. If the $[HCO_3^-]$ is to remain constant, the $[H^+]$ must increase by the same factor (i.e. from 40 to 80 mmol/l *or* pH 7.40 to 7.10). In the human organism, buffers diminish any change in $[H^+]$ resulting from variations in PCO_2 (Part 5-2). An acute rise in PCO_2 (*acute respiratory acidosis*, Part 5-3) is accompanied by a corresponding generation of H^+, but almost all of these are buffered by phosphate buffer and negatively charged proteins. When the change in $[H^+]$, calculated as a fraction of the initial value, is *smaller* than the change in PCO_2, the changes in $[HCO_3^-]$ are also smaller and the rise is no longer proportional to the changes in PCO_2.

An increased production of H^+ from acids other than CO_2 (as in non-volatile acids creating a metabolic acidosis, Part 5-3) stimulates ventilation and leads to increased excretion of CO_2 and reduced PCO_2. As PCO_2 *decreases* while $[H^+]$ *increases*, the HCO_3^- is reduced.

As **K_a** and **k** are both constants, it can be deducted from the equations above that

- If $[H^+]$ stays *constant (e.g. in compensated hypercarbia,* fig 5-9*)*, a change in PCO_2 changes the $[HCO_3^-]$ by the *same fraction*, i.e. the $[HCO_3^-]/PCO_2$ ratio stays constant.
- If $[H^+]$ increases *(e.g. reduced pH in metabolic acidosis)*, the $[HCO_3^-]/PCO_2$ ratio must be reduced, i.e. the $[HCO_3^-]$ change as a fraction is *lower* than that of PCO_2.
- If $[H^+]$ decreases *(e.g. increased pH, metabolic alkalosis)*, the $[HCO_3^-]/PCO_2$ ratio must increase i.e. the fractional $[HCO_3^-]$ change as a fraction is *higher* than that of PCO_2.

See also calculation examples at the end of this Part.

Dissociation of lactic acid. The calculated values in table 5-1 are based on the dissociation of acids in *pure water*; the presence of buffers changes the relationship between the concentrations of conjugate base **A^-** and non-dissociated acid **HA** substantially.

Lactic acid ($C_3H_6O_3$) has a pKa of 3.85, i.e. a weak acid when dissociated in water but sometimes called a strong acid as it is fairly well dissociated in normal blood (3548:1 at pH 7.40 (16), see also table 5-2). This means that the measurement of lactate is representative for the lactic acid concentration. A weak acid with a low degree of dissociation in pure water can therefore behave as a much stronger acid in the presence of buffers.

Using the Henderson-Hasselbalch equation for calculations.

At normal arterial blood pH of 7.40, and with the pK_a of carbonic acid (H_2CO_3) at body temperature equal to 6.1, the equation becomes

$$\mathbf{7.40 = 6.1 + \log \frac{[HCO_3^-]}{[k \times PCO_2]}}$$

and the log of the ($[HCO_3^-]$/ [k x PCO_2]) ratio becomes 1.3.

The antilog of $10^{1.3}$ is 19.95, and the concentration of HCO_3^- ions is about *20 times higher* than the term [k x PCO_2] at normal arterial pH. As a normal PCO_2 gives a denominator of about 1.22 mmol/l (see above), the normal $[HCO_3^-]$ becomes (19.95 x 1.22) = 24.3 mmol/l.

If the actual pH of the blood is 7.00, the equation becomes

$$\mathbf{7.00 = 6.1 + \log \frac{[HCO_3^-]}{[k \times PCO_2]}}$$

making the log $[HCO_3^-]$/[k x PCO_2] ratio 0.9. As the antilog of $10^{0.9}$ is 7.94, the concentration of HCO_3^- ions at a pH of 7.00 is about *8 times higher* than that of [k x PCO_2]. Table 5-2 shows calculations for other pH values in the pH 6.1 to 7.8 range. The **$[A^-]$/[HA]** ratios show that H_2CO_3 would be an ideal buffer at pH 6.1; at blood pH of 7.4, it is far from ideal, but the capacity for efficient respiratory regulation of the conjugate base as CO_2 compensate for this. The **$[A^-]$/[HA]** ratio for lactic acid within the survivable range of blood pH shows that this weak acid has virtually no buffering capability in the human organism.

		H_2CO_3. pKa = 6.10		$C_3H_6O_3$. pKa = 3.85	
pH	**$[H^+]$ nmol/l**	**log $[A^-]$/[HA]**	**$[A^-]$/[HA]**	**log $[A^-]$/[HA]**	**$[A^-]$/[HA]**
7.8	16	1.7	**50.1**	3.95	**8913**
7.7	20	1.6	**39.8**	3.85	**7079**
7.6	25	1.5	**31.6**	3.75	**5623**
7.5	32	1.4	**25.1**	3.65	**4467**
7.4	40	1.3	**20.0**	3.55	**3548**
7.3	50	1.2	**15.8**	3.45	**2818**
7.2	63	1.1	**12.6**	3.35	**2239**
7.1	79	1	**10.0**	3.25	**1778**
7.0	100	0.9	**7.9**	3.15	**1413**
6.9	126	0.8	**6.3**	3.05	**1122**
6.8	158	0.7	**5.0**	2.95	**891**
6.7	200	0.6	**4.0**	2.85	**708**
6.6	251	0.5	**3.2**	2.75	**562**
6.5	316	0.4	**2.5**	2.65	**447**
6.4	398	0.3	**2.0**	2.55	**355**
6.3	501	0.2	**1.6**	2.45	**282**
6.2	631	0.1	**1.3**	2.35	**224**
6.1	794	0	**1.0**	2.25	**178**

Equation: **pH** = pKa + log $[A^-]$/[HA].

Table 5-2. *Calculated dissociation of carbonic acid (H_2CO_3) and lactic acid ($C_3H_6O_3$) in H_2O at different pH values, using the Henderson-Hasselbalch's equation.*

Calculation of bicarbonate concentrations.

Using the equation on pg 353, a bedside calculation of $[HCO_3^-]$ can be carried out by ***i)*** calculating the increase or fraction in PCO_2 and $[H^+]$ from normal values ($[H^+]$ must be calculated from the pH value, see above) ***ii)*** carrying out the division and ***iii)*** multiplying the result with the normal value of $[HCO_3^-]$. If the PCO_2 doubles (a factor of 2 as above) and the $[H^+]$ increase from 40 nmol/l (*pH* 7.40) to 60 nmol/l (*pH* 7.22), i.e. $[H^+]$ increases by 50% *or* a

factor of 1.5 due to buffering, the [HCO3-] can be calculated by multiplying the normal values by the change, expressed as a *fraction of normal levels* (**green**) of PCO_2 and $[H^+]$

$$[HCO_3^-] = (K_a \times k) \times \frac{2 \text{ x } PCO_2}{1.5 \text{ x } [H^+]}$$

$$or\ [HCO_3^-] = (K_a \times k) \times 1.33 \text{ x } \frac{PCO_2}{[H^+]}$$

i.e. the actual $[HCO_3^-]$ *increases by a fraction of 1.33 of normal* and is 33% higher than normal.

If the $[H^+]$ increase from 40 nmol/l to 60 nmol/l, a fraction of 1.5, as a result of metabolic acidosis (see Part 5-2 and above), and the acidosis-induced increased ventilation reduces PCO_2 from 5.3 kPa to 3.55 kPa (i.e. a fraction of about 0.67 of normal, the $[HCO_3^-]$ will be

$$[HCO_3^-] = (K_a \times k) \times \frac{0.67 \text{ x } PCO_2}{1.5 \text{ x } [H^+]}$$

$$or\ [HCO_3^-] = (K_a \times k) \times 0.44 \text{ x } \frac{PCO_2}{[H^+]}$$

i.e. the $[HCO_3^-]$ *decreases by a fraction of 0.44 of normal* and is 44% of the normal value.

If the reduction in PCO_2 to 3.55 kPa was due to primary acute hyperventilation, the $[H^+]$ would be reduced to around 32 nmol/l (*pH* ≈ 7.50) or a *fraction* of 32/40=4/5 or 0.8 of normal, the calculated $[HCO_3^-]$ would be

$$[HCO_3^-] = (K_a \times k) \times \frac{0.67 \text{ x } PCO_2}{0.8 \text{ x } [H^+]}$$

$$or\ [HCO_3^-] = (K_a \times k) \times 0.83 \text{ x } \frac{PCO_2}{[H^+]}$$

i.e. the $[HCO_3^-]$ *decreases by a fraction of 0.83 of normal* and is 83% of the normal value.

In extreme metabolic acidosis of many hours duration and maximal respiratory compensation, the PCO_2 may be reduced to levels in the 1.2 kPa (9 mmHg) range (a fraction of 1.2/5.3 = 0.226 of normal). If the final $[H^+]$ is increased to 60 nmol/l (*pH* 7.22), (a fraction of 1.5 times normal), the $[HCO_3^-]$ would be

$$[HCO_3^-] = (K_a \times k) \times \frac{0.226 \text{ x } PCO_2}{1.5 \text{ x } [H^+]}$$

$$or\ [HCO_3^-] = (K_a \times k) \times 0.15 \text{ x } \frac{PCO_2}{[H^+]}$$

i.e. the $[HCO_3^-]$ *decreases by a fraction of 0.15 of normal* and is 15% of the normal value. Such extreme values are seldom observed in clinical medicine.

5-2. ACID-BASE BALANCE IN THE HUMAN ORGANISM

Generation of acids during the normal metabolic state.

Acids are generated intracellularly, transported away by the microcirculation and *either* excreted by lungs/kidneys *or* utilized by other metabolic processes. The acids generation by the combustion of the nutrients included in a normal western diet can roughly be grouped into

- **Intermediate metabolic products** like **lactic acid** *and* **keto acids,** whose generation under normal circumstances is balanced by their removal through either *further metabolic degradation* or *utilization as substrates* for synthesis of other molecules. Excretion of such acids from the body is therefore not necessary under normal conditions. Their normal levels in the blood are low (a few mmol or fractions of a mmol/l), but levels may increase 10-30 times during unfavorable metabolic circumstances (e.g. insufficient supply of O_2 *or* carbohydrates) or disease. If normal conditions for their utilization can be rapidly re-established (e.g. for *lactic acid:* adequate O_2 supply to tissues or cessation of strenuous muscular activity, for *keto acids:* insulin treatment of diabetic ketoacidosis, adequate nutrition after starvation), they can re-enter their normal metabolic pathways. After this, their concentration may be normalized within hours (see lactacidosis below, also Part 2-4).
- **End products of metabolism** that must be *excreted* from the organism at *the same rate as their generation* if the $[H^+]$ in body fluids is to remain stable. These may be categorized as **volatile** or **non-volatile acids**.
  - The major **volatile acid** is the gas **carbon dioxide** (**CO_2**). After diffusing *out* of the cells, *through* the interstitial fluid, and *into* the capillaries, the gas enters the erythrocytes where most of the molecules are *hydrated* to carbonic acid (fig. 5-5). When the erythrocytes reach the alveoli, this reaction is reversed; the dissolved CO_2 diffuses from plasma to alveolar gas and is exhaled. The efficiency of CO_2 excretion depends on the ***i)*** *blood flow* through the lungs, ***ii)*** the pulmonary *ventilation volumes,* and ***iii)*** the efficiency of the *alveolar gas exchange* (i.e. the V/Q ratios).
  - The two major **non-volatile acids** are **sulfuric acid** *and* **phosphoric acid**. Their generation varies with the diet, meat is rich in both sulphur (**S**) and phosphorus (**P**). They must be excreted as acids dissolved in urine and are therefore often called "**renal acids**".

Exogenous agents (whether inhaled, ingested, or infused) may also induce metabolic acidosis, by ***i)*** *generating acids* during their metabolism, ***ii)*** *introducing* exogenous acids directly into the organism, or ***iii)*** *interfering* with the normal metabolism of endogenous acids (Part 5-3).

Production of *lactic acid* and *CO_2* varies with changes in the metabolic rate and may increase several fold within few minutes. Accordingly, they are the acids associated with the most rapid rise of **$[H^+]$** in body fluids when the ratio between generation and elimination changes. As CO_2 is excreted by the lungs, it is the only acid metabolite where the concentrations in arterial and venous blood may differ substantially (Part 3-3).

A surplus of acids with increased levels of **CO_2 in the arterial blood** as the *primary* disturbance is defined as **respiratory acidosis**, increased **CO_2** *without* acidosis (e.g. compensated chronic hypoventilation) is termed *hypercapnia*. Increased levels of other, nonvolatile acids, endogenous as well as exogenous, are traditionally denoted **metabolic acidosis;** in persons with normal respiratory function, it is usually accompanied *hyperventilation* and *reduced* CO_2 levels.

Metabolites with base properties. A primary generation of a *surplus of bases* compared to acids does not normally occur in the body. Ingestion of large quantities of special foodstuffs (especially a strict vegetarian diet), drugs, or other agents of a basic nature may, however, induce a reduction in $[H^+]$ (alkalosis) by increasing the concentration of base (17). In some diseases (see Part 5-3), pathological increases in the excretion of H^+ ions (e.g. increased renal- and gastrointestinal loss) surpasses their generation, leaving an excess of base in the body fluids.

GENERATION OF ACIDS AND THEIR TRANSPORT FROM CELLS TO BLOOD

The generation of acid metabolites occurs intracellularly, they must first cross the cell membrane and then diffuse through the interstitial fluid and across the capillary wall before dissolving in the capillary blood and becoming part of the venous blood. The consequences of an imbalance between their generation and elimination are, however, traditionally measured in the samples of arterial blood. To preserve both intracellular and extracellular $[H^+]$ within relatively narrow limits, acid metabolites must be removed from the blood at the same rate as they are generated. Until this is accomplished, an increase of plasma $[H^+]$ is modified by the buffer effect of phosphoric acid, bicarbonate as well as Hb and albumin molecules (see below).

GENERATION OF CO_2 BY AEROBIC METABOLISM.

CO_2 and water (H_2O) are the major end products of the mitochondrial aerobic metabolism through the citric acid cycle (also called the *tricarboxylic cycle* or *Krebs cycle,* Part 2-1). The function of this cycle is intimately connected with the consumption of O_2, any change in aerobic metabolic activity that increases the O_2 consumption results in a parallel increase in CO_2 production. The normal ratio between CO_2 production and O_2 consumption (the respiratory quotient, RQ) is 0.8 but may vary from ≈ 0.7 (preferential metabolism of fats) to ≥1.0 (preferential metabolism of carbohydrates).

The bulk of CO_2 is dissolved as a gas and diffuses into the capillary plasma along a gas concentration gradient (fig. 5-4). Even if some of the CO_2 molecules react with water (is *hydrated*) to carbonic acid, this process is both slow and limited. Only a small fraction of the dissolved CO_2 molecules are hydrated until they enter the erythrocytes, where they are exposed to the intracellular enzyme *carbonic anhydrase* (**CA**). The hydration reaction then becomes virtually instantaneous (milliseconds or parts of a millisecond):

$$\mathbf{CO_2 + H_2O \xrightarrow{(CA)} H_2CO_3,}$$

after which the $\mathbf{H_2CO_3}$ rapidly dissociates into $\mathbf{H^+}$ and $\mathbf{HCO_3^-}$ ions.

This reaction reduces the concentration of dissolved CO_2 molecules, and thus the gas pressure of CO_2, in the plasma, which helps to maintain the *cell-to-capillary diffusion gradient* for CO_2 (fig. 5-4).

Most of the HCO_3^- created by the H_2CO_3 dissociation diffuses *out* of the erythrocytes and *into* the plasma; to conserve electroneutrality both intra- and extracellularly, an equal number of chloride (Cl^-) ions enter the erythrocytes from the plasma (the chloride shift (18)). The absolute increase of HCO_3^- ions in the blood, relative to a PCO_2 increase, is modest; in short-term experiments where P_aCO_2 was increased in volunteers breathing gas with increased content of CO_2, the HCO_3^- increase within the clinical range was found to be approximately 0.75 mmol/l for each kPa of PCO_2 (or 0.1 mmol/l per mmHg) (19).

Almost all of the H^+ ions liberated by the hydration of CO_2 and subsequent dissociation of H_2CO_3 within the erythrocytes are immediately bound by negatively charged proteins, mostly Hb. Their

binding to **Hb molecules** reduces the affinity of these molecules for O_2, allowing them to release more O_2 to the tissues (Part 2-3). This protein buffering is so efficient that the normal concentration of free H^+ ions in the microcirculatory (and venous) blood is close to 1:600 000 of the concentration of HCO_3^- ions.

While the *speed* of CO_2 hydration is determined by the presence of carbonic anhydrase, the *amount* of dissolved CO_2 that is transformed into HCO_3^- depends on the ***i)*** pressure of CO_2 gas, ***ii)*** blood temperature and ***iii)*** intraerythrocyte acidity. Some of the CO_2 molecules entering the erythrocytes also bind directly to the Hb molecules as *carbamino compounds*; the Hb molecules that have released their O_2 (are *desaturated*) have an increased capacity for forming such compounds. As the pressure of CO_2 in the tissues is higher than that in the arterial blood arriving in the capillaries, the normal direction of the reaction above in the microcirculation is to the right.

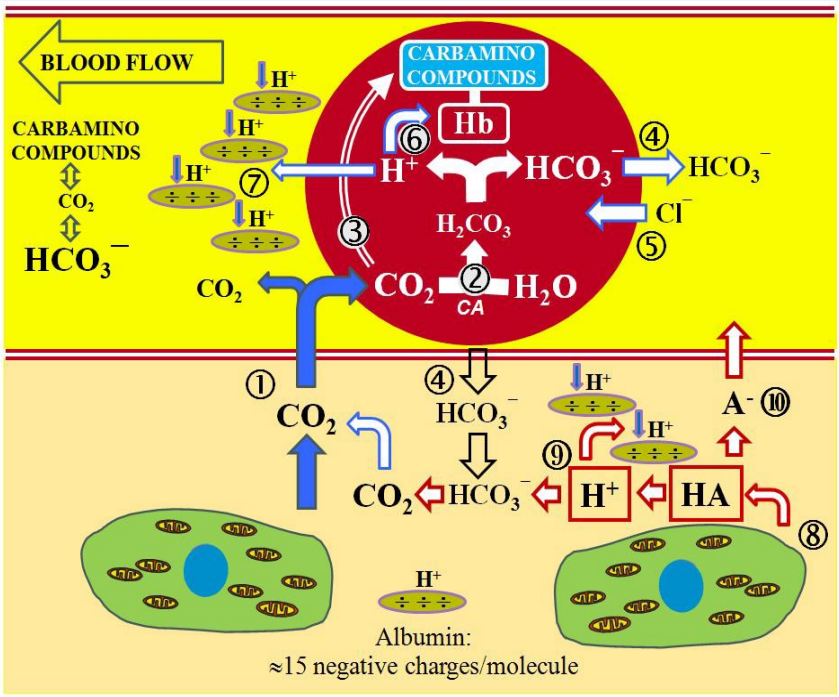


Figure 5-4. *Tissue generation and transport of acid metabolites. The* **CO_2** *molecules diffuse freely along a gas concentration gradient out of the cells, through the interstitial fluid* ① *and into the plasma before entering the erythrocytes* ②**.** *Once inside the erythrocytes, they are exposed to the enzyme carbonic anhydrase (CA), the reaction* **$CO_2 + H_2O \Rightarrow$** (CA) **$\Rightarrow H_2CO_3$** *then becomes virtually instantaneous and most of the CO_2 molecules are hydrated. Some* **CO_2** *molecules undergo a reversible chemical reaction with amino acids in the Hb molecule, forming* ***carbamino compounds*** ③. *The* **H_2CO_3** *dissociates immediately into equal amounts of* **H^+** *ions and bicarbonate ions:* **$H_2CO_3 \rightarrow H^+ + HCO_3^-$**. *Most of the* **$HCO_3^-$** *diffuse out of the erythrocytes into plasma* ④ *and are replaced by chloride ions* (**Cl^-**) ⑤ *to preserve electroneutrality. Part of the* **HCO_3^-** *ions subsequently diffuse from plasma into the interstitial fluid along the concentration gradient* ④*. Almost all the* **H^+** *ions bind to negatively charged proteins; either Hb molecules inside the erythrocytes* ⑥ *or albumin molecules in the plasma or interstitial space* ⑦*.*
Non-volatile acid *metabolites* (**HA**) *and their dissociation products* (**H^+** *and the conjugate base* **A^-**) *diffuse out of the cells along a concentration gradient* ⑧*. Most of the* **H^+** *ions either bind to* **HCO_3^-** *and generate additional CO_2 gas, or bind to albumin molecules in the interstitium* ⑨*.*

Under normal conditions, the CO_2 content of mixed venous blood (i.e. the *weighted mean* CO_2 content of the blood leaving the microcirculation of the various tissues) consists of *dissolved CO_2 gas*, *carbamino compounds*, and *bicarbonate (HCO_3^-) ions* (20), the latter represents close to 90% of the total CO_2 in arterial blood (see also Part 2-3). The balance between HCO_3^- and the other forms of CO_2 changes with the blood $[H^+]$ as described by the Henderson-Hasselbalch's equation.

Consequently, venous blood contains more CO_2 and is always slightly more acid than arterial

blood; the normal veno-arterial PCO_2 difference of 0.6 kPa (4-5 mmHg) may result in a veno-arterial HCO_3^- difference as low as ≈ 0.5-1 mmol/l; i.e. under most conditions, the bicarbonate levels in venous and arterial blood are *almost* the same. The difference in venous and arterial acidity may, however, be grossly amplified under conditions of *increased metabolism* without a matching increase in blood flow (e.g. heavy exercise), or during conditions of *reduced blood flow* without a matching decrease in metabolism (e.g. circulatory shock, see "High flow states" and "Low flow states").

GENERATION AND TRANSPORT OF ENDOGENOUS NON-VOLATILE ACIDS.

The non-volatile acids (e.g. lactic acid, keto acids, sulfuric acid, *and* phosphoric acid) are produced continuously by most cells (fig. 5-4); they dissolve in the intracellular fluid and dissociate, in full or partly, into equal amounts of H^+ ions and the acid's conjugate base (A^-) (see Part 5-1). Intracellular buffers (primarily phosphate buffer, see below) bind H^+ and prevent large shifts in intracellular $[H^+]$ when the metabolic rate changes *or* the diffusion gradient diminishes. Under normal circumstances, both H^+ and A^- ions diffuse along a concentration gradient *out* of the cells, *through* the interstitial fluid (where most of the H^+ is buffered by albumin and bicarbonate) and *into* the microcirculation (fig. 5-4).

The production of some of them may be substantially increased during physical exertion (lactate), starvation (keto acids), and disease (both). The acidosis-driven increase in ventilation cause increased amounts of CO_2 to be excreted by the lungs and the blood P_aCO_2 decreases; the bulk of free H^+ ions produced by the metabolic processes react with HCO_3^-. Some H^+ ions bind to negatively charged albumin molecules in the interstitial fluid; a tiny amount diffuses along an increased H^+ concentration gradient into the plasma.

The excretion of non-volatile acids by the kidneys is a slow process, the difference in their concentration between venous and arterial blood is therefore small and of little clinical significance.

Excretion of CO_2 in the lungs.

When the venous blood reaches ventilated alveoli, the PCO_2 in the alveolar gas is slightly lower than that in the arriving venous blood (i.e. 5.3 kPa (*40 mmHg*) vs ≈ 6 kPa (*45 mmHg*)). The CO_2 then diffuses into the alveoli along the gas pressure gradient. When the CO_2 concentration in plasma and within the erythrocytes falls; the reaction occurring in the tissues is reversed and runs to the left; CO_2 is formed during *dehydration* of H_2CO_3:

$$\downarrow CO_2 + H_2O \xleftarrow{(CA)} H_2CO_3 \leftarrow \downarrow H^+ + \downarrow HCO_3^-$$

Most of the H^+ ions involved in this reaction are released from their binding sites on the Hb molecules, which then increase the Hb molecule's affinity for O_2 (a leftward shift of the HbO_2 curve) and augment their capacity for O_2 uptake in the lungs..

The *efficiency of CO_2 excretion* in the lungs depends on

- The available *pulmonary gas exchange surface* (reduced by alveolar edema, increased alveolar dead space and high V/Q conditions (see also Part 4-3)) and the *ventilation volumes.*
- The *CO_2* gas *pressure gradient* (PCO_2) between plasma and alveoli (reduced in hypoventilation, increased in hyperventilation (see also Part 4-2)).

Diffusion of CO_2 across the alveolar-capillary membrane is not a limiting factor *per se* (21).

Under normal conditions, the magnitude of the ventilation is finely tuned by the peripheral and central chemoreceptors to maintain the CO_2 in arterial blood within narrow limits (Part 4-1). During hypoventilation or *no* ventilation (apnea), CO_2 will continue to pass from blood to alveolar

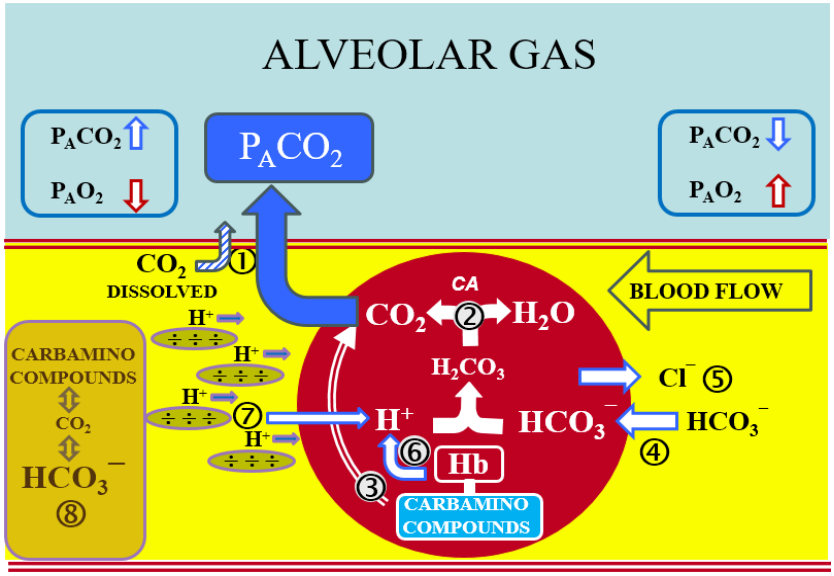


Figure 5-5. *Alveolar excretion of CO_2. The* **PCO_2** *of the mixed venous blood is higher than that in alveolar gas and CO_2 molecules diffuse along a gas concentration gradient from plasma to alveoli ①. The reduced concentration of* **CO_2** *molecules in plasma makes the intraerythrocyte reaction:* **$CO_2 + H_2O \leftarrow H_2CO_3 \leftarrow H^+ + HCO_3^-$** *proceed to the left ②. The carbamino compounds also release CO_2 ③. When the intraerythrocyte* **HCO_3^-** *concentration decreases,* **HCO_3^-** *from the plasma enters through the erythrocyte cell membrane ④ and* **Cl^-** *ions leaves to preserve electroneutrality ⑤. The reduction in* **H^+** *concentration that accompanies the regeneration of* **CO_2** *from* **HCO_3^-** *is mostly compensated for by its release from Hb ⑥. Albumin also release* ***H^+*** *ions ⑦, and the total H^+ binding capacity of the protein buffers increase. The balance between the three states of CO_2 in the blood changes ⑧, with a reduction in the percentage of CO_2 bound as carbamino compounds in arterial blood.*

gas as long as the PCO_2 of the venous blood is higher than that in the alveoli. A step-by-step schematic figure depicting CO_2 excretion in the lungs is presented in fig. 5-5.

If the pulmonary excretion of **CO_2** *exceeds* the tissue generation, both venous and alveolar **PCO_2** decrease. The **HCO_3^-** and **H^+** are then also reduced (respiratory alkalosis), equilibrium between pulmonary capillaries and alveoli occurs at a lower blood **PCO_2** level and the blood-to-alveoli PCO_2 gradient (and thus the efficiency of gas excretion) is reduced. Insufficient ventilation and CO_2 excretion, on the other hand, eventually establishes a new equilibrium between generation and excretion at a higher blood PCO_2 level (fig 5-8); **HCO_3^-** and **H^+** are then both increased (respiratory acidosis).

Generation and fate of common non-volatile acids.

Lactic acid.

Lactic acid is a product of glycolysis, the O_2-independent initial step in carbohydrate metabolism (see also Part 2-1). In mature erythrocytes, which lack mitochondria, it is the physiological metabolic end product. In other cells, it is an intermediate product that becomes fully metabolized in the citric acid cycle; the small amounts leaving muscle cells (22) are used for gluconeogenesis, mainly by the liver. Normal production is ≈ 1 500 mmol per day, and the normal blood concentrations of 0.3-1.5 mmol/l.

In any condition where the rate of tissue glycolysis runs faster than that of the citric acid cycle, lactic acid accumulates in the cells with increased spillover to the blood. If the magnitude of such spillover is greater than the combined ability of the liver (most important), kidneys, and active muscle to metabolize it, lactic acid accumulates in the blood and produces lactacidosis. Increased production of lactic acid in limited areas of the body may not be detectable in the general bloodstream as long as the ability of other organs to metabolize lactate remains intact. In the normal organism, excess lactate generated by short-term intense exertion or hypoperfusion states can

be metabolized to CO_2 and H_2O within hours if conditions favoring aerobic metabolism are rapidly re-established. In severe liver failure, however, an uncontrollable increase in lactic acid may occur (23).

Keto acids.

The metabolism of fats generates small amounts of ketone bodies. Of the three most common species, two (*β-hydroxyl butyric acid* and *acetoacetic acid*) are weak acids. Normal production varies, but may be as high as several thousand mmol per day. Their normal blood concentration is low; if the intracellular supply of carbohydrates becomes insufficient for the maintenance of normal metabolic activity (e.g. diabetes, fasting, starvation), the cells turn to increased combustion of fats, and the concentration of keto acids in the blood increases. After the re-introduction of a sufficient supply of carbohydrates to the cellular metabolism, the keto acids are metabolized to CO_2 and water.

Sulfuric- and phosphoric acid.

Sulfuric acids are generated by the process of metabolizing sulfur-containing amino acids (primarily methionine and cysteine) present in the food (24). Phosphorus is present in high concentrations in animal cells; many types of food, especially meat and others rich in proteins, are important sources of phosphorus. Sulfuric acid (H_2SO_3) and phosphoric acid (H_3PO_4), respectively, must ultimately be dissolved in urine and excreted by the kidneys ("renal acids"); renal failure may lead to the accumulation of these acids in the organism.

BUFFER SYSTEMS IN THE BODY FLUIDS

An acute (i.e. arising within minutes to few hours) *excess of H^+ ions* in the body fluids may be due to

i) **increased production** of volatile or non-volatile acids due to changes in the metabolic processes *or* to the presence of exogenous acids, *or*

ii) a **reduced capacity for metabolism** or **excretion** such acids.

The **initial defense** against a rise in $[H^+]$ is accomplished by the **buffers**. These are often divided into intracellular- and extracellular buffers; all buffers will, however, co-operate in the regulation of $[H^+]$ in body fluids. The H^+ that is buffered by bicarbonate can rapidly be excreted from the organism as CO_2 with the expired gas. The binding of free H^+ by other buffer molecules is, *per se*, a temporary solution; to regain the buffer capacity of the body fluids, the buffered H^+ must subsequently be excreted from the organism as H^+ or NH_4^+ dissolved in the urine. If these mechanisms fail and the buffer capacity becomes saturated, the rise in $[H^+]$ may rapidly become dangerous.

Intracellular buffers.

- **Bicarbonate** (fig. 5-4). As most of the bicarbonate is generated within the erythrocytes (see above), there is a bicarbonate gradient from blood to cells. The intracellular concentration of bicarbonate in tissue cells is, therefore, lower than in the extracellular fluid and the blood (approx. 10 mmol/l vs 24 mmol/l) (25).

In *addition to bicarbonate*, the main intracellular buffers in tissue cells are

- **Intracellular proteins** containing a net excess of negative charges at the physiological pH range (**$Prot^- + H^+ \rightarrow HProt$**) *and*
- The **phosphate buffer system** (mainly **$HPO_4^{--} + H^+ \rightarrow H_2PO_4^-$**). The intracellular concentration of phosphorus is 10-20 times higher than the extracellular one; phosphate buffers are therefore of great importance inside the cells but have a limited capacity in the extracellular fluid space.

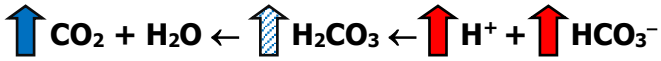
Excess acid (i.e. the non-buffered increase in **H^+**) subsequently spills over into the interstitial fluid and blood passing through the microcirculation, where they may combine with extracellular buffers (see below).

Ion exchange mechanisms across the cellular membrane, where electrolytes (mainly K^+) are exchanged for H^+ when the intracellular acidity increases, are not buffer systems *per se* but do have a protective effect on cellular function as they prevent the intracellular accumulation of H^+ ions to become dangerous. Such exchange is not universal in all types of acidosis but varies with the mechanism for H^+ generation (26, 27).

Extracellular buffers: the central role of bicarbonate.

The **HCO_3^-** ions are the major buffer in the extracellular space (see fig. 5-4). Due to the continuous production of CO_2 by the tissue cells, the gas diffuses into the microcirculatory blood along a concentration gradient and increases the plasma PCO_2. After diffusion into the erythrocytes and becoming exposed to carbonic anhydrase, the CO_2 reacts with water and the equation runs to the right, increasing the bicarbonate levels

An acute increase in blood or tissue **H^+** (severe metabolic acidosis) combined with rapid administration of substantial amounts of **HCO_3^-** (e.g. i.v. administration of sodium bicarbonate, **$NaHCO_3$**) can, for a short period, reverse the direction of this reaction and increase the intracellular CO_2:



The CO_2 produced during such reversal of the reaction adds to the metabolically generated CO_2 and raises the amount of CO_2 dissolved in *tissues* and *venous blood*; the increased intracellular CO_2 level *may* increase the intracellular acidity temporarily (28) but only under low- or no-flow conditions (29).

Whether or not the arterial PCO_2 also increases depends on the efficiency of the pulmonary excretion of CO_2 (see above). Increased venous PCO_2 (augmented CO_2 production *or* low microcirculatory flow) and low alveolar PCO_2 (due to the acidosis-stimulated increase in ventilation) increase the magnitude of the PCO_2 gradient between blood and alveoli and augment the efficiency of CO_2 diffusion from blood into the airways. A *primary reduction in the number of dissolved CO_2 molecules* (as when the primary disturbance is CO_2 excretion *in excess* of its production) also makes the reaction run to the left (see Part 5-3, respiratory alkalosis).

Acidosis is a powerful stimulus to increase ventilation, the peak minute ventilation can increase by a factor of 10-20 times baseline. In persons with normal respiratory function, increased excretion of CO_2, and thus of H^+, starts within seconds after an $[H^+]$ increase in arterial blood *or* intracerebral fluid. The reduced level of CO_2 in the blood drives the reaction to the left (pg 351);

more H^+ ions then combine with HCO_3^- and are excreted by the expired gas. The normal amount of HCO_3^- ions is considerable, but is rapidly reduced when the H^+ increases and the PCO_2 decreases (Part 5-1), as *more* CO_2 is excreted than that generated by the metabolic processes.

In persons with *limited* or *no ability to increase their alveolar ventilation* in response to increased $[H^+]$ and P_aCO_2, the efficiency of the $H^+ + HCO_3^-$ buffer system is low and rapidly becomes even less effective as the P_aCO_2 rises. If buffering of metabolic acidosis with infusions of bicarbonate (as $NaHCO_3$) are attempted in such patients, there is only a minor reduction of $[H^+]$; PCO_2 in all fluid compartments increases, and arterial blood gases will show a mixed respiratory and metabolic acidosis instead of a purely metabolic one.

Extracellular buffers: the role of negatively charged proteins ($prot^-$).

Amino acids are the building blocks of proteins; some of them (the branched amino acids) have side chains with either a negative (Arginine, Histidine, Lysine) or a positive (Aspartic acid, Glutamic acid) charge at a normal pH of around 7.40. Depending on the type of amino acids incorporated in the proteins, the distribution of their side chains gives the protein molecules either a *net positive*, *neutral,* or *net negative charge*. The latter type of molecules function as *anions* and can act as buffers. The two main buffer proteins with such properties are **hemoglobin (Hb)** and **albumin**, which bind H^+ molecules primarily due to the effect of their Histidine side chains.

Albumin is the major protein buffer in interstitial fluid. It is also important in plasma; in blood as a whole, however, **Hb** is the major protein buffer. Even if the Hb molecules are located *inside* the erythrocytes and should thus be classified as an intracellular buffer, their function is so inti-mately connected with the buffer capacity of the blood that the Hb molecules have a central place in the acid-base balance of the blood as a whole (fig. 5-4).

While HCO_3^- ions combine with free H^+ ions on a 1:1 basis (see above), protein molecules have many sites (i.e. the amino acid side chains) that can combine with H^+ ions. **Hb** and **albumin** molecules have approximately the same molecular weight (≈ 64 500 vs ≈ 66 500 Da); the number of negatively charged side chains available for combining with H^+ ions varies with the surrounding pH. At normal arterial pH, the **Hb molecule** has some **26-32 negative charges** (30, 31); the **albumin** molecule has about **15 negative charges** (32). At normal Hb and albumin concentration in the blood, the combined buffer capacity of these proteins amounts to approximately 14 - 16 mEq/L (see Gambles diagram, fig. 5-6 below). Other types of proteins (mostly the globulins) have a close to equal number of positive and negative charges of their side chains at normal pH and have little or no buffer capacity. A pathological increase in the production of monoclonal gamma globulins with either net positive or negative charges can, however, alter the buffer systems of the body and create an acid-base imbalance (33).

Ions and smaller molecules pass relatively freely across the capillary walls in most of the microcirculation (except for capillaries in the brain), the buffer capacity of negatively charged proteins in the blood and interstitial fluid is therefore often considered as one unit. The normal volume of the interstitial fluid is close to twice that of the blood, and the contribution of Hb as a buffer in the total extracellular fluid compartment is normally equivalent to around 1/3 of the blood value, i.e. if the blood Hb is 15 g/dl, the Hb contribution to the total extracellular buffer capacity is equivalent to 5 g/dl (34) in the extracellular fluid. A substantial reduction in the amount of *proteins* (Hb and/or albumin) can result in an increased concentration of free H^+ ions, which creates an acidosis even when the generation of acid metabolites is normal and the mechanisms for the excretion of H^+ ions are intact (see metabolic acidosis below).

Cerebrospinal fluid has a low buffer capacity.

An exception from the above is the conditions governing the acid-base state of the cerebrospinal fluid (CSF). This fluid is in close contact with the central chemoreceptors, and the $[H^+]$ in this fluid is of great importance for the regulation of pulmonary ventilation (Part 4-1). The normal CSF contains no Hb molecules and the albumin concentration is less than 1% of that in plasma (normal levels 0.304 g/l vs 40.8 g/l (35)), accordingly, it contains virtually no protein buffers. In addition, the tightness of the endothelial junctions in the brain microcirculation (the "blood-brain barrier") makes the diffusion of H^+ and HCO_3^- ions between blood and CSF very slow; molecules of CO_2, however, diffuse rapidly between them.

This makes bicarbonate the only buffer of importance in the CSF fluid. In the absence of cerebral damage or hypoxia, alterations in CO_2 are thus the only factor that changes the $[H^+]$ in the CSF on a short-term basis. As there is no carbonic anhydrase in the CSF, the hydration and dehydration of CO_2 (i.e. the generation of carbonic acid and its subsequent dissociation, see above) proceed at a much slower rate than in the blood.

The law of electroneutrality, Gambles diagram, and Buffer Base.

According to the law of electroneutrality, the sum of molecules with positive charges in a solution (i.e. cations and protein molecules with net positive charges) and the sum of those with negative charges (anions *and* protein molecules with net negative charges) must be equal. An exception from the principle of electroneutrality is the fluid layer close to cell membranes, where ion transporter proteins can establish a local cation/anion imbalance and create an electrical potential across the membrane.

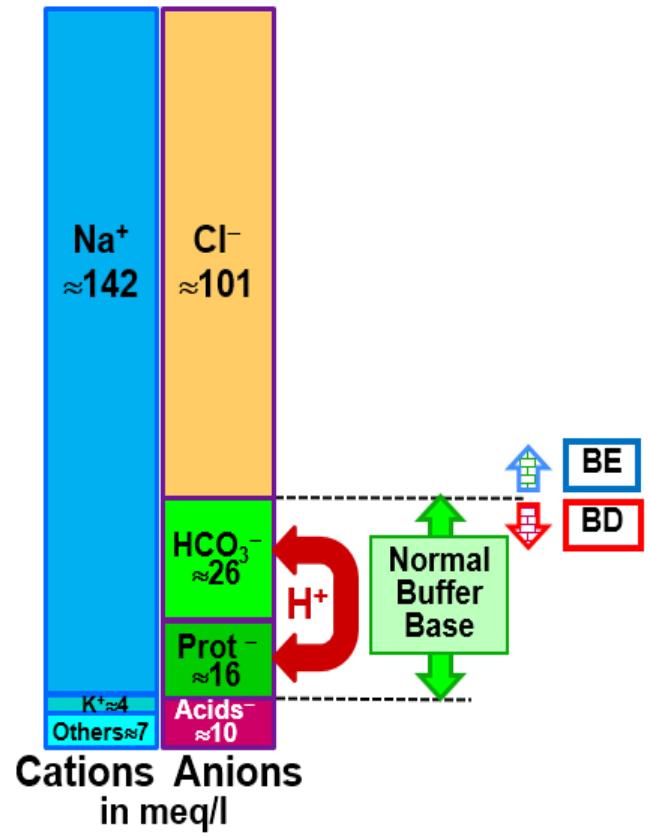


Figure 5-6. *Gambles diagram, depicting the extracellular concentrations of major cations and anions relative to the normal buffer capacity. Changes in $[H^+]$ is buffered by both* **HCO_3^-** *and* **prot$^-$**, *which together constitute the Buffer Base* **(BB).**

The use of the electroneutrality principle to illustrate the balance of electrolytes and buffers in blood during acid-base derangements (see fig. 5-6) was first employed by J.L. Gamble using a so-called "Gamble diagram" in a publication in 1925 (36) and has later been modified by others (37). A central feature of this modified diagram is the portrayal of the two elements that constitute most of the buffer capacity in the blood, i.e. the *sum of bicarbonate* and *protein buffers,* as an unit called the **Buffer Base (BB)**. An *increased BB* is called **Base Excess** (**BE**), and a *reduced* BB is called a **Base Deficit** (**BD**), the latter is often reported as a **negative BE** (**- BE**).

BE and BD were originally calculated directly by measuring the amount of acid or base needed to titrate a blood sample back to a normal pH of 7.40. This method does not accurately reflect the state in the total extracellular fluid, as the albumin concentrations in blood and interstitial fluid are different and the Hb molecules are restricted to the blood. In modern blood gas analyzers, the calculation of BB, BE and BD is based on empirical equations with corrections for the effect of Hb. The modified Gamble diagram and the BB concept are utilized for explaining how various types of acid-base derangements affect the $[H^+]$ and the concentration of buffers in the blood – see Part 5-3 for examples.

On the use of milliequivalents vs millimoles in Gambles diagram.

Although the most important electrolytes are univalent, some of the ions in the extracellular fluid, and the Hb/albumin molecules as well, have more than one charge. As a result, the principle of electroneutrality is difficult to illustrate by comparing the concentrations of all charged molecules using units like mmol/l, mg/dl, etc.). The older unit milliequivalents/liter (meq/l) (i.e. the number of positive or negative charges carried by the specific ions in the solution multiplied by their concentration in mmol/l), as used by Gamble in his original diagram, is rational for this particular purpose.

The normal content of acids (i.e. of their conjugate bases) in extracellular fluid.

Under normal conditions, there is a relatively fixed amount of various non-volatile acids in the blood (lactic acids, keto acids, sulfuric- and phosphoric acids, as well as others). These acids are largely dissociated at normal extracellular pH; their concentration is therefore not of acids *per se*, but as their negatively charged conjugate bases (**A^-**, "Acids" in fig. 5-6). Most of these conjugate bases, except for lactate, are not routinely analyzed; under normal circumstances their sum (see fig. 5-6) represents a total negative charge equivalent to about 10 meq/L.

Other extracellular anions important for the acid-base balance.

The major anion in the blood is chloride (Cl^-), whose normal concentration of ≈ 100 mmol/l equals ≈ 100 meq/l. The normal sum of negative charges (Cl^- + buffers + conjugate bases of acids) is in the 150-155 meq/l range. Changes in Cl^- concentration, especially when the difference between concentrations of Na^+ and Cl^- (Δ (Na^+ – Cl^-)) is altered, is an important diagnostic indicator in metabolic acid-base disturbances (see Part 5-3: Anion Gap, Stewart principle). Also, Cl^- is important for the renal compensation of some types of acid-base disturbances.

Extracellular cations important for the acid-base balance.

The major cations, Na^+ and K^+, are univalent so that their concentration in mmol/l equals their charge in meq/l. In normal concentrations (≈142 mmol/l and ≈ 4.5 mmol/l, respectively), their sum represent about 95% of the total positive charges of the cations. The rest of the cations are Ca^{++}, Mg^{++}, and various other substances whose concentrations in blood are below 1 mmol/l. The K^+ concentration changes with the $[H^+]$ (see above); also, it is important for the renal compensation of some types of acid-base disturbances (see below).

Footprints of H^+ concentration change in the Gamble diagram.

A major limitation of this diagram is that the $[H^+]$ cannot be realistically depicted. The sum of conjugate bases of the acids normally present in the extracellular fluid ("fixed" acids) is around 10 meq/l (see above), and the normal $[H^+]$ of 40 nmol/l is approximately 250 000 times lower. Although the generation of H^+ ions due to the dissociation of acids (lactic acid, keto acids) is equal to the increase in the conjugate bases ("$Acids^-$", see above), almost all excess H^+ ions are

neutralized by the buffer systems. Such buffering keeps the $[H^+]$ in the extracellular fluid within the survivable range of 16 nmol/l to 500 nmol/l (corresponding to pH 7.80 and 6.30, respectively, refs. 38, 39, see also fig. 5-1). The changes in the concentration of dissociated acids are, however, indicated by changes in the concentration of buffers and in $[Cl^-]$ *relative to* $[Na^+]$ (see Part 5-3).

5-3. DISTURBANCES IN THE ACID-BASE EQUILIBRIUM

H^+ ion concentration and clinical implications.

Any change in the ratio between production and excretion of volatile or non-volatile acids, *or* a change in the buffer capacity, alters the $[H^+]$ in body fluids. Most such changes can be detected in arterial blood. A table of H^+ concentrations in blood pertinent to human medicine, with their corresponding pH values is shown below (table 5-3). This table also shows the $[H^+]$ and pH values expected from acute deviations in *either* blood CO_2 levels (respiratory acidosis/alkalosis, see below) *or* changes in the buffer capacity due to variations in the concentration of non-volatile acids in the blood (metabolic disturbances); the values shown are calculated employing the Siggaard-Andersen alignment nomogram (40). Comments on the clinical significance in the table refer to values in arterial blood; pH levels in venous blood, interstitial- and intracellular fluid are generally lower (see below for details).

H^+ *nmol/l*	pH	PCO_2*	BE#	H^+ *nmol/l*	pH	PCO_2*	BE#	H^+ *nmol/l*	pH
15	7.82			80	7.10	18.2	-19	240	6.62
20	7.70	*1.6*	*+24*	90	7.05	*> 22*	-22	280	6.55
25	7.60	*2.4*	*+15*	100	7.00	*?*	*≈ -26*	320	6.49
32	7.50	*3.6*	*+7*	125	6.90	*?*	*≈ -32*	360	6.44
40	7.40	*5.3*	*0*	140	6.85			400	6.40
50	7.30	*8.0*	*-7*	160	6.80			440	6.36
63	7.20	*12.2*	*-13*	178	6.75			480	6.32
70	7.15	*14.3*	*-17*	200	6.70			500	6.30

Table 5-3. *Relation between H^+ concentrations, pH values and respiratory/metabolic disturbances. Values (in kPa) shown in the PCO_2* columns are the levels corresponding to values in the pH column if no metabolic compensation has occurred (Buffer Base unchanged, Base Excess ≈ 0). Values (in mmol/l) in the BE# column correspond to the pH values where a metabolic derangement induce acute changes in Buffer base (positive or negative in mmol/l) if no respiratory compensation has occurred (i.e. if PCO_2 remains normal at 5.3 kPa (40 mmHg)). Values are approximate, assuming Hb = 15 g/dl. At lower Hb values, i.e. reduced amount of buffer capacity, the actual pH is reached at lower PCO_2 and BE values. PCO_2 and BE values corresponding to a pH outside the 7.05 – 7.70 range cannot be reliably calculated by this method (see below for more about Buffers and Base Excess). Color codes:*
Extreme alkalosis. *Common, not dangerous per se.*
Negative effects of acidosis on various organs. *May indicate serious disease and life-threatening conditions, C_aO_2 can be substantially reduced despite normal PO_2 values. White numbers indicate levels outside the reported survivable range.*

Imbalances between acids and bases in the organism: definitions and classification.

In clinical medicine, deviations from the normal acid-base balance usually refer to changes in *arterial blood* if not specified otherwise. Regardless of etiology, a deviation is denoted

- **Acidosis,** if the **$[H^+]$** is increased **above 45 nmol/l (pH ≤ 7.35),** *or*
- **Alkalosis,** if the **$[H^+]$)** is decreased **below 35 nmol/l** (**pH ≥ 7.45).**

In some groups of patients, especially those with circulatory failure, additional analyses of acid-base and blood gases (O_2, CO_2) in samples drawn simultaneously with the arterial from a CVC (central venous sample, low precision) or the right ventricle *or* PA (mixed venous blood, high

precision) may provide basis for an estimate of whether or not the ratio between O_2 *supply to* and the O_2 *consumption by* the organism as a whole, the **$DO_2/\dot{V}O_2$ ratio**, is satisfactory.

The healthy organism has a considerable capacity for re-establishing a normal $[H^+]$ by adjusting ventilation and renal function when an imbalance between H^+ ion production and elimination arises,*or* when the buffer concentration changes. Even after a successful normalization of $[H^+]$, the CO_2 and buffer content of the blood (see below), sometimes also the Na^+- Cl^- balance (see Hyperchloremic acidosis), may still be outside the normal range. Such changes can be considered footprints of the initial disturbance, and allow identification of the mechanisms precipitating the primary acid-base disorder. An acute acidosis caused by a short-term accumulation of lactic acid or keto acids may not, however, leave any laboratory footprints if the normalization of $[H^+]$ is achieved within hours by rapid elimination of the excess acid through normal metabolic pathways.

To avoid confusion, acid-base derangements where an initial increase or decrease in $[H^+]$ have become compensated by such processes should not be described as acidosis or alkalosis if compensatory mechanisms have succeed in re-establishing a normal arterial pH. They should be referred to as acid-base derangements or disturbances caused by the primary acidosis/alkalosis, compensated by pulmonary and/or renal mechanisms,*or* by the state of CO_2 balance (e.g. hypercapnia, hypocapnia). The interpretation of acid-base disturbances according to the views of Stewart (see below) allows, however, for defining derangements as acidosis or alkalosis even when associated with a normal $[H^+]$ (41).

Acid-base imbalances are further classified by their **etiologies** (in disturbances involving non-volatile acids often supplemented with the name of the causative agent) and **duration**. In *acute* disturbances there has been no or limited time for renal compensation, in *chronic* disturbances, compensatory mechanisms may have changed the initial deviation of $[H^+]$ towards normal, while other footprints of the initial disturbance persist.

Classification of acute acid-base disturbances by etiology (see also Interpretation of blood gas analysis, Part 5-4).

- **Respiratory acidosis**. This acidosis is associated with*increased arterial PCO_2* , the*primary cause* of the $[H^+]$ increase is a *failure of the lungs to excrete CO_2* at the same rate as its tissue production. When the PCO_2 concentration in the alveolar gas (P_ACO_2) increases, *more* CO_2 is excreted per ml of expired gas; a new balance between production and excretion of CO_2 is subsequently established but at a higher P_aCO_2 and P_ACO_2 level than previously. If the condition becomes chronic, *renal compensation* may reduce or normalize $[H^+]$ while the PCO_2 remains elevated, the condition is then a **compensated hypercapnia**.
- **Respiratory alkalosis.** This alkalosis is associated with*decreased arterial PCO_2* , the primary cause of the $[H^+]$ decrease is an excretion of CO_2*in excess* of the tissue production rate. To re-establish equilibrium between CO_2 production and excretion, the decreased CO_2 concentration in the alveolar gas (and also in arterial blood) cause *less* CO_2 to be excreted by each expiration. If chronic, *renal compensation* may normalize $[H^+]$ while PCO_2 remains reduced, the condition should be denoted a **compensated hypocapnia**.
- **Metabolic acidosis.** Acute acidosis is most often caused by an *imbalance* between the rate of generation of *H^+ from non-volatile acids* and their elimination. As acidosis stimulates ventilation, it is usually accompanied by a *reduced P_aCO_2* and *consumption of buffers,* leading to a reduced buffer base. A primary loss of base (as HCO_3^-) may, according to the law of

mass action (see Part 5-1), also lead to an increase the blood [H^+]. This mechanism is a less common cause of metabolic acidosis and evolves more slowly.

- **Metabolic alkalosis.** This alkalosis is usually caused by an increased loss of H^+ from the gastrointestinal tract or kidneys. It is associated with a compensatory *normal or increased* PCO_2 and a positive BE.
- **Combined (or mixed) metabolic-respiratory acidosis**. A *combination of respiratory and metabolic acidosis*, i.e. increased [H^+] *and* PCO_2 *plus* a reduced buffer base.
- **Combined (or mixed) metabolic-respiratory alkalosis**. A *combination of respiratory and metabolic alkalosis, i.e.* reduced [H^+] *and* PCO_2 *plus an* increased buffer base (rare).
- **Mixed derangements**. In some situations, especially when an acute acid-base disturbance becomes superimposed on a more chronic one (e.g. chronic metabolic alkalosis with superimposed lactacidosis, chronic respiratory acidosis with acute hyperemesis), the [H^+] may be close to normal or even reduced. Two (or more) disturbances with different etiologies and opposite effects may nullify each other in their effect on H^+ ion concentration (see below).

Acute and chronic conditions.

- Most acid-base disturbances commonly seen in acute- and ICU medicine have an *acute phase* (i.e. evolving within minutes/hours, with time for partial respiratory compensation but little or no time for adjustment of renal function) and a *chronic, compensated phase* (i.e. after maximal respiratory and/or renal adjustment has occurred). An *intermediate phase* represents the period *after* the initiation of renal adjustments and more efficient respiratory compensation but *before* the full effect has been achieved. An exception is metabolic alkalosis, which usually evolves over many hours/days, and where an acute phase is seen only after infusion or ingestion of exogenous base.
- In *chronic* disturbances, where the renal compensatory mechanisms have been active for several days, the H^+ concentrations may deviate only moderately, or not at all, from the normal range (42). Any remaining deviation is, however, usually to the side expected from the original disturbance (i.e. acidosis or alkalosis). If a chronically elevated P_aCO_2 that is well compensated by renal mechanisms is suddenly normalized by controlled ventilation, the metabolic compensation to chronic hypercarbia may wrongly be interpreted as a primary metabolic alkalosis.

THREE LINES OF DEFENSE AGAINST DEVIATIONS IN [H^+].

The three mechanisms for maintaining the [H^+] within acceptable limits when an imbalance between H^+ generation and excretion proceed along different timelines.

The immediate reaction: buffering of H^+ or release of H^+ by buffers.

Buffers (see above) in the intracellular *and* interstitial fluid *and* blood binds or releases H^+ ions within *milliseconds*. An acute excess of free H^+ ions of any etiology can be neutralized instantaneously and *almost* completely by the body's buffer systems; conversely, a reduction in H^+ concentration leads to the immediate release of H^+ ions from the buffers. The buffering of H^+ ions from non-volatile metabolic acids by buffers other than bicarbonate is, *per se*, a temporary solution, as the conjugate bases of the acids are not excreted from the body in the acute phase. In chronic conditions, bone and other tissues may also act as buffers, although with a low efficiency (43).

The acute response: respiratory adaption.

Acute adjustment of ventilation (i.e. changing the pulmonary excretion of CO_2 and thus of H^+ – see fig. 5-7, A and B), is the most important response mechanism for eliminating excess H^+ ions from the body in the initial phase. As every molecule of CO_2 may be envisioned as consisting of an H^+ ion bound to a bicarbonate ion through its hydration (see above), increasing the excretion of CO_2 eliminates more H^+ ions from the organism, while reducing ventilation retains H^+ ions within the organism. The normal arterial concentration of bicarbonate and H^+ is 24 x 10^{-3} mol/l (24 mmol/l) and 40 x 10^{-9} mol/l (40 nmol/l), respectively, excretion of each mmol of bicarbonate as CO_2 gas eliminates 1 000 000 H^+ ions. The adjustment of ventilation is strongly affected by the concentration of free H^+ ions in the blood *and* cerebrospinal fluid; the ventilatory line of defense is activated within seconds to minutes and is *limited* only by the person's *ventilation capacity* and the *ventilation-perfusion conditions* in the lungs (see Part 4-2).

Changes in PCO_2 resulting from changes in ventilation also change the H^+ ion concentration surrounding the central chemoreceptors (Part 4-1); the acute ventilatory response therefore seldom compensates fully for a metabolic disturbance. In severe metabolic acidosis, hyperventilation may reduce the PCO_2 to levels as low as 1.2 kPa (9 mmHg) (44).

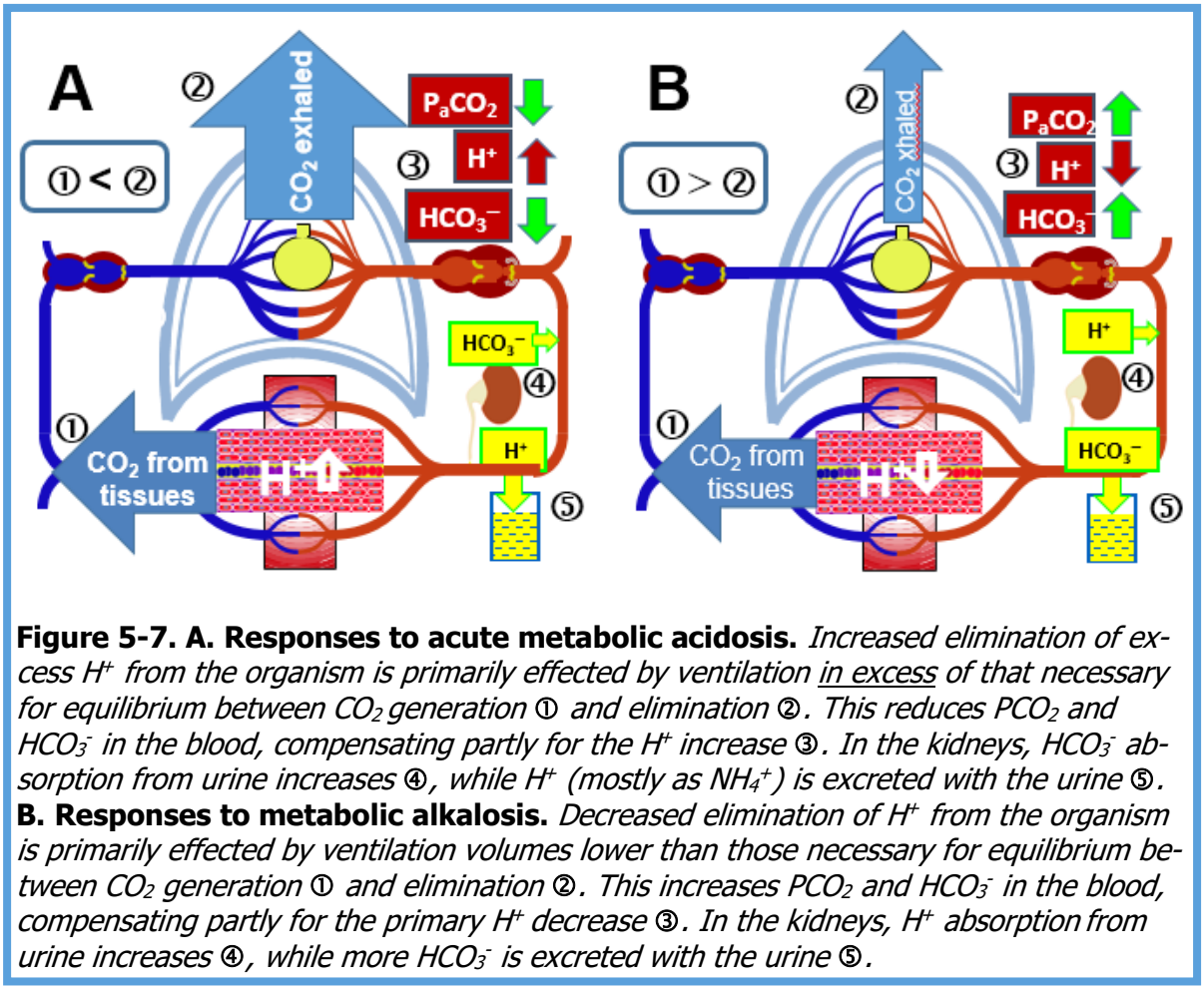


Figure 5-7. A. Responses to acute metabolic acidosis. *Increased elimination of excess H^+ from the organism is primarily effected by ventilation <u>in excess</u> of that necessary for equilibrium between CO_2 generation ① and elimination ②. This reduces PCO_2 and HCO_3^- in the blood, compensating partly for the H^+ increase ③. In the kidneys, HCO_3^- absorption from urine increases ④, while H^+ (mostly as NH_4^+) is excreted with the urine ⑤.*
B. Responses to metabolic alkalosis. *Decreased elimination of H^+ from the organism is primarily effected by ventilation volumes lower than those necessary for equilibrium between CO_2 generation ① and elimination ②. This increases PCO_2 and HCO_3^- in the blood, compensating partly for the primary H^+ decrease ③. In the kidneys, H^+ absorption from urine increases ④, while more HCO_3^- is excreted with the urine ⑤.*

The major *limitation of this mechanism is the non-selective 1:1 excretion or retention of H^+ and bicarbonate ions*, causing it to become less efficient as a defense against metabolic acidosis as the concentration of bicarbonate in the blood and the alveolar CO_2 is reduced by the increased CO_2 excretion *and* the reduced HCO_3 dissociation due to increased $[H^+]$. *If the cause of increased H^+ ions is a primary respiratory failure, this line of defense is non-functional.*

The subacute response: adaption of tubuli cell function.

Renal compensation. Augmenting renal *excretion of H^+ ions* and *resorption of bicarbonate ions* in acidosis, and *vice versa* in alkalosis, starts rapidly. In opposition to the non-selective 1:1 excretion of H^+ and HCO_3^- by the lungs, the tubuli cells can selectively excrete and reabsorb either of these ions in accordance with the acid-base disturbance present in the arterial blood. The rates of excretion and resorption are, however, slow, *limiting their importance in acute states.* In acidosis, excretion of free $\mathbf{H^+}$ ions *as such* in the urine is limited; the larger part is excreted as $\mathbf{NH_4^+}$ ions, produced from the metabolism of glutamate in the proximal tubuli cells (45)(see fig. 5-7). Several days may be needed to reset the acid-base and buffer balance of the body by this mechanism. Renal compensation is the main defense of the body against chronic acid-base disorders; it is, however, not always perfect even in healthy kidneys. A deficit of K^+ and/or Cl^- in the blood may inhibit the ion exchange mechanisms in the renal tubuli; hormones like aldosterone and angiotensin II affects the reabsorption/excretion process and are necessary for the effective excretion of H^+ ions (46). *The renal compensation mechanisms cease to function, partly or completely, in renal dysfunction or failure.*

Extracorporeal devices. In modern medicine, shunting part of the circulating blood through external devices for elimination of CO_2 (ECMO, CO_2 eliminators) may correct respiratory acidosis, various dialysis systems may correct acidosis caused by increased $[H^+]$ due to the "renal" acids and most exogenous agents that induce acidosis.

ACID-BASE DERANGEMENTS: CLINICAL CONDITIONS

Physiological metabolic acidosis.

Normal activities of healthy persons may lead to a substantial acid-base imbalance; the *physiological lactacidosis* resulting from extreme physical exertion for less than an hour may be more severe than that evolving during shock or CPR for cardiac arrest (see lactacidosis below). *Physiological ketoacidosis* (during fasting or insufficient nutritional carbohydrate supply) may be substantial, but develops more slowly (hours or days, weeks for starvation) and is less severe than that caused by insulin deficiency. Both types are self-limiting if the underlying cause can be remedied, in which case they seldom have lasting negative consequences.

Acute acidosis in severe diseases.

In many emergencies and acute diseases, acidosis constitutes part of the pathophysiological picture. Life-threatening metabolic acidosis may develop rapidly; in acute circulatory failure, especially when compounded by hypoxemia, severe lactacidosis may be found within minutes (47). Acute respiratory failure with respiratory acidosis can also develop rapidly (e.g. severe asthma attacks, acute airway obstruction, drug overdose) and is often compounded by hypoxemia, leading to a severe combined respiratory and metabolic acidosis (48). During involuntary apnea, life-threatening tissue hypoxia develops long before acidosis due to CO_2 accumulation becomes a problem. The P_aCO_2 can be expected to increase by about 0.5-0.8 kPa (4-6 mmHg) per minute in unconscious or deeply sedated persons (49, 50).

Even modest increases in muscular activity, however, increase O_2 consumption and production of CO_2 by 2-300% (Part 2-1). Both severe hypoxemia and increased PCO_2 levels will therefore develop much faster during apnea due to acute airway occlusion in the awake state (increased $\dot{V}O_2$ due to generalized agitation, and maximal effort by respiratory muscles) than during deep sedation. A simple rule of thumb is that an acute increase in P_aCO_2 to 20 kPa (150 mmHg)

increases the [H^+] corresponding to a pH between 7.00 and 7.10 if hypercapnia is *the sole* derangement (table 5-3) and there has been no time for renal compensation.
Alkalosis is seldom an acute threat to survival; the hyperacute alkalosis with loss of consciousness and convulsions during psychogenic hyperventilation may be dramatic but is usually self-limiting. In acute and intensive care medicine, there is consequently more focus on dangers associated with acidosis than on alkalosis.

The presence of acidosis in a single sample of arterial blood has, *per se,* little prognostic value. On the other hand, changes in blood gases, when correctly interpreted (see below), are important diagnostic tools and may function as a gauge of the *severity of disease* as well as the degree of *disturbance in the ratio between DO_2 and VO_2.* In the absence of obvious etiologies, *unexplained lactacidosis* should also raise suspicion of possible *mitochondrial dysfunction; thiamine deficiency* may also cause an otherwise unexplained lactacidosis.

Acidosis due to drug effects and intoxications. In some clinical conditions, e.g. *metformin intoxication* , the magnitude of acid-base deviations from normal during the acute phase shows poor or no association with the patient outcome (51). In *methanol intoxication* , the presence and degree of acidosis (first due to formic acid, later followed by lactic acid) in blood samples depend on which stage of the disease the samples are acquired (52, 53). In general, severe acidosis signals a major disturbance in organ function or metabolism, and is associated with a poorer prognosis (54). A review of various types of drugs that can precipitate metabolic acidosis is presented in ref. (55).

Metabolic acidosis in other conditions. Even moderate deviations from the normal acid-base status that *per se* do not represent a danger to the organism, may be associated with severe disease (56). In some types of disease, even modest acidosis (e.g. degree of lactacidosis in hemorrhagic shock or serious infections) seems to have prognostic value (57, 58, 59). The rate of *lactate clearance* in response to appropriate therapy may, however, reflect the degree of metabolic impairment or damage to mitochondrial function, and be a better prognostic indicator than the initial lactate values *per se* (60, 61, 62).

Other causes of accumulation of acids in the blood.

Exogenous substances (e.g. methanol and other alcohols, various drugs, and toxins) may also generate acids when ingested, inhaled, or injected. A **loss of base** shifts the acid-base balance in favor of increased [H^+] in aquatic fluids and thus also in the fluids of the body (see the law of mass action above and metabolic acidosis below).

WAYS TO IDENTIFY AND QUANTIFY ACID-BASE DERANGEMENTS

In clinical medicine, two traditional concepts, and one more recently introduced, are used to explain the effect of acid-base disturbances on buffers and electrolytes in the blood (see fig. 5-7 to 5-9). Calculation of *Base Deficit and Base Excess* (see below) compare the effect respiratory and metabolic disturbances has on the concentration of buffers in the blood and the magnitude of buffer consumption. Calculation of the *Anion Gap* (see below) utilize the difference between [Na^+] and ([Cl^-] + [bicarbonate]) to discriminate between metabolic acidosis caused by increased concentration of non-volatile acids (i.e. the conjugate bases, Part 5-1) and those caused by pathological loss of base. The *"Strong Ion" calculations* of Stewart compares the difference (the "Gap") between the sum of highly dissociated cation and anion concentration, and the calculated sum of buffers in plasma, using the difference between the calculated values as an indicator of

whether the concentration of non-volatile acids is increased or not. The pathophysiological mechanisms constituting the base for such calculations are described below.

The buffer base (BB) concept and its utilization for diagnosis.

This method for describing changes in the acid-base balance by employing the impact of variations in $[H^+]$ on the concentration of buffers was introduced in the late 1940-ties by Singer and Hastings and developed further by Siggaard-Andersen and co-workers (63, 64, 65). The *main value* of this concept lies in its ability to *discriminate* between *acute* acid-base derangements due to *primary changes in* **arterial CO_2 (**respiratory *acidosis/alkalosis)* and *primary changes in the blood concentration of* **non-volatile acids** *or* **buffers** (metabolic *acidosis/alkalosis)* . The *combined capacity* of HCO_3^- ions and protein$^-$ molecules for binding H^+ ions represents most of the total buffer capacity of the extracellular fluid (see fig. 5-6 above).

If the quantity of BB in a given patient is *lower* than normal due to the binding of excess H^+ by the buffers, the reduction of buffer capacity (i.e. the difference between the patient's BB and the normal value) represents a *base deficit* (**BD**). Such reduction is usually due to either ***i)*** **increased binding of H^+ ions** by the buffer anions (i.e. formation of more HA – H_2CO_3 and proteins with neutral charges), ***ii)*** **increased external loss of bicarbonate** or ***iii)*** **low levels of protein buffers**. If the concentration of buffers is *higher* than normal, the difference becomes a *base excess* (**BE**), which implies that the **H^+ concentration is decreased** *or* **that renal reabsorption of bicarbonate is increased.** Overenthusiastic infusions of bicarbonate (as $NaHCO_3$) may cause the same picture. In acute disease or trauma, the magnitude of buffer consumption in patients *without* muscle spasms induced by a rise in lactic acid production is also a measure of the severity of the underlying tissue hypoxia.

An increase in H^+ ions due to the *accumulation of non-volatile acids* is buffered by both HCO_3^- and *protein*$^-$ simultaneously, resulting in a reduction of both and thus of the BB, creating a BD (see above). If the cause of the H^+ increase is a *rise in PCO_2*, the *protein*$^-$ buffers H^+ ions analogous to that for metabolic acids above. The CO_2 increase leads to an *increase* in HCO_3^- which is almost equal to the *decrease* in *protein*$^-$; the *sum of buffers* is still normal but their *relative concentration* change. The capacity of the protein component of the buffer system depends on the number of buffer protein molecules in the blood; a major reduction in either Hb (anemia) *or* plasma protein content (e.g. severe hypoalbuminemia) *or* both reduces the buffer capacity (66, 67). Ideally, a change in both should be corrected for when the BB is calculated (see below). An increased release of H^+ ions (in response to H^+ ion decrease due to external loss) from one or both of these buffers increases the Buffer Base.

The BB-BE concept in the diagnosis of the type of acid-base imbalance.

In the equations describing different types of acid-base derangements on buffer concentration, the *primary changes* in are indicated by *red arrows*, *secondary changes* by *blue.*

Acute Respiratory Acidosis: a primary increase in dissolved CO_2 and P_aCO_2. In the event of a primary increase of CO_2 in the blood, the rightward shift in the $CO_2 + H_2O$ equation below increase the quantity of dissociated H^+ and HCO_3^- at the same rate.

Almost all the H^+ ions resulting from the hydration of CO_2 to H_2CO_3 and its subsequent dissociation become buffered by the negatively charged proteins (Prot-H); the remaining $[H^+]$ increase is in the nanomol/l range but have a substantial effect on the blood pH (see Part 5-1):

$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$ ⇑ **Hydration** of CO_2 and H_2CO_3 dissociation.

⇑ **Prot-H** ← $H^+ + Prot^-$ ⇓ **Increased** binding of H^+ to protein anions.

The reduction in protein$^-$ will then be of approximately the same magnitude as the increase in HCO_3^-; the *sum* of HCO_3^- and protein$^-$ change only marginally. BB is close to normal and the calculated **BE does not change** significantly (fig. 5-8).

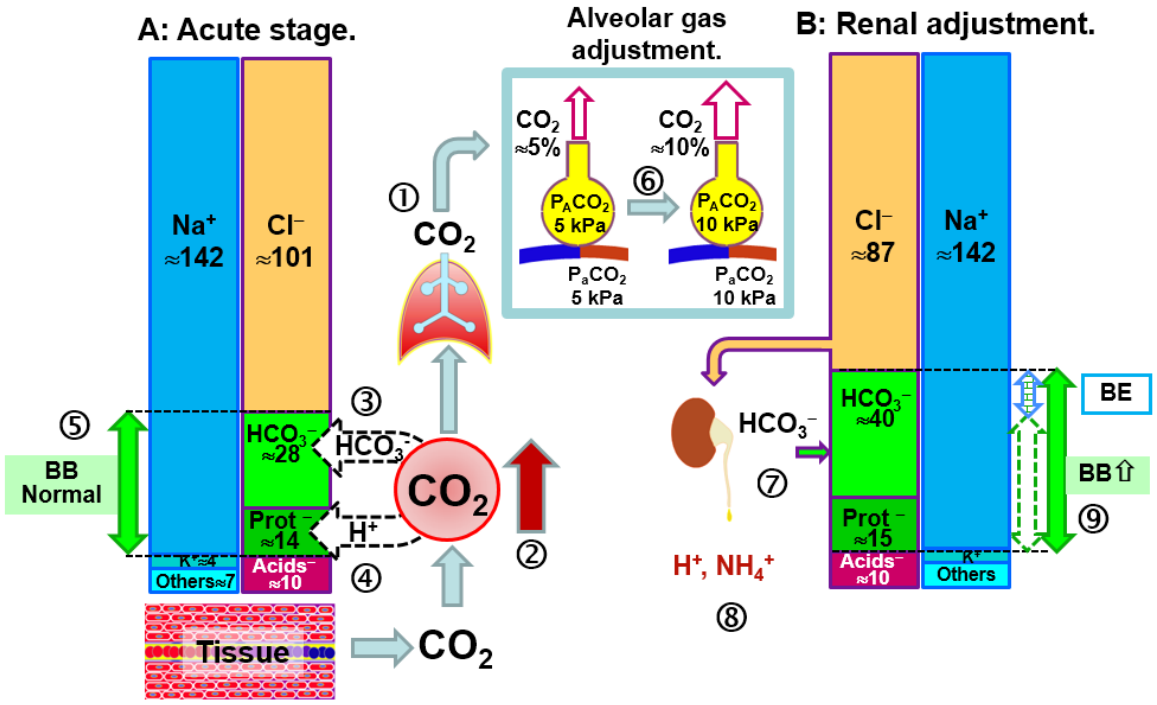


Figure 5-8: Respiratory acidosis.

A. Acute stage

When pulmonary excretion of **CO_2** ① *becomes insufficient relative to that produced by tissues, blood* **CO_2** *levels (and thus* **PCO_2**) *increase* ②. *This generates increased amounts of* **HCO_3^-** ③ *and* **H^+** ④; *virtually all the increased* **H^+** *ions binds to buffer proteins in blood and interstitial fluid (Hb/albumin). The decrease in* **prot**$^-$ *is almost equal to the increase in* **HCO_3^-**; *the sum of buffers, the Buffer Base (***BB***) is therefore unchanged* ⑤ *(BE ± 0) until renal compensatory mechanisms become effective.*

Pulmonary adaption.

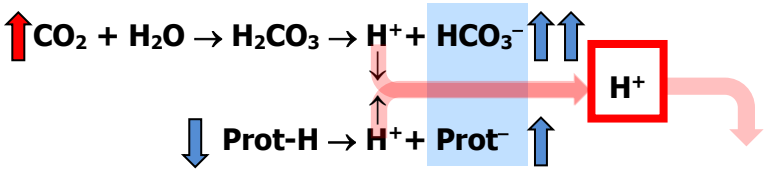
In perfused alveoli, increased blood **PCO_2** *is accompanied by an equal increase in* **P_ACO_2**; *the number of* **CO_2** *molecules pr. ml of expired gas then increase* ⑥ *until a new balance between* **CO_2** *production and excretion is established at a higher* **P_ACO_2** *and* **P_aCO_2** *level.*

B. Renal adaption.

In normal kidneys, renal tubuli cells respond to acidosis by increased reabsorption of **HCO_3^-** *in exchange for* **Cl^-** ⑦. *Simultaneously, excretion of* **H^+** *ions (mostly as NH_4^+ ions) increase* ⑧; *the reduction in* **[H^+]** *release* H^+ *ions from buffer proteins which again increase the concentration of* **prot**$^-$. *As* **HCO_3^-** *is already increased, and increase further with falling* [H^+], *the total* **BB** *increases, establishing a Base Excess* (**BE**) ⑨.

Chronic CO_2 increase with renal compensation: partially compensated respiratory acidosis *or* compensated hypercapnia with normal pH.

If the condition becomes chronic, increased amounts of H^+ ions are excreted by the kidneys during the following days; when the acidosis is reduced the reaction runs to the right and the HCO_3^- increases further (see also fig. 5-8). If this results in a pH within the normal range, the condition is no longer an acidosis, but a *compensated hypercapnia* . As a result of H^+ normalization, the *ratio* between HCO_3^- and PCO_2 (see Part 5-1) returns to normal.



Renal H^+ elimination – days.

Simultaneously, the amount of $prot^-$ increases as the proteins release H^+ when its level in the fluid surrounding them decreases due to renal excretion. The **BB increases**, with a positive base excess (+BE), (fig. 5-8).

PCO_2 and bicarbonate changes in hypercarbia/respiratory acidosis.

The concentration of bicarbonate varies with changes in PCO_2 and H^+; variations are *proportional* to changes in PCO_2 and *inversely proportional* to changes in H^+ according to the equation (see also Part 5-1)

$$[HCO_3^-] = (K \times k) \times \frac{PCO_2}{[H^+]}$$

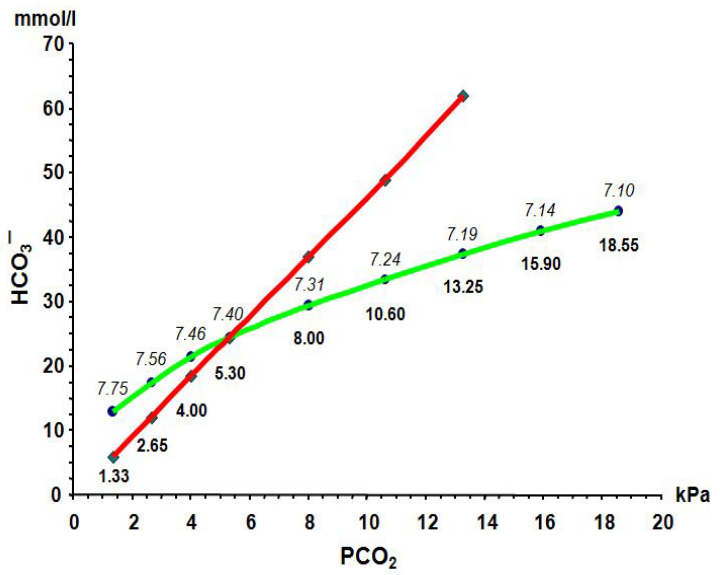


Figure 5-9. *Bicarbonate levels in acute and chronic respiratory alkalosis/acidosis. Green curve: Acute phase with no renal compensation, calculated pH values corresponding to acute changes in PCO_2 (bold numbers below green line) are shown in italics above the green line. Red line: Chronic conditions, if renal compensation mechanisms has resulted in a pH close to normal (7.40).*

If an acute respiratory acidosis turns into a chronic hypercarbia and renal adjustments reduce the $[H^+]$ while the PCO_2 stays elevated, the HCO_3^- must increase. As the pH becomes closer to normal, the ratio between bicarbonate and PCO_2 changes.

Such pH normalization will occur in most patients with chronic PCO_2 levels below 8 kPa (60 mmHg) and normal renal function, some may have a normal or even subnormal $[H^+]$ at even higher CO_2 levels (42). The expected relationship between PCO_2 and bicarbonate during acute and chronic states (the latter after the renal compensation results in a normal H^+ concentration) are depicted in fig. 5-9.

Metabolic acidosis: Acidosis due to increased levels of non-volatile acids.

In metabolic acidosis (e.g. lactic acid, keto acids, renal acidosis, exogenous agents), the increased [H^+] is a result of dissociation of increased concentrations of non-volatile acid metabolites. The [H^+] bind to *both* protein$^-$ and HCO_3^- molecules; consequently, the concentration of both is reduced and the **BB decreases**. This creates a base deficit (BD *or* – BE). More CO_2 is

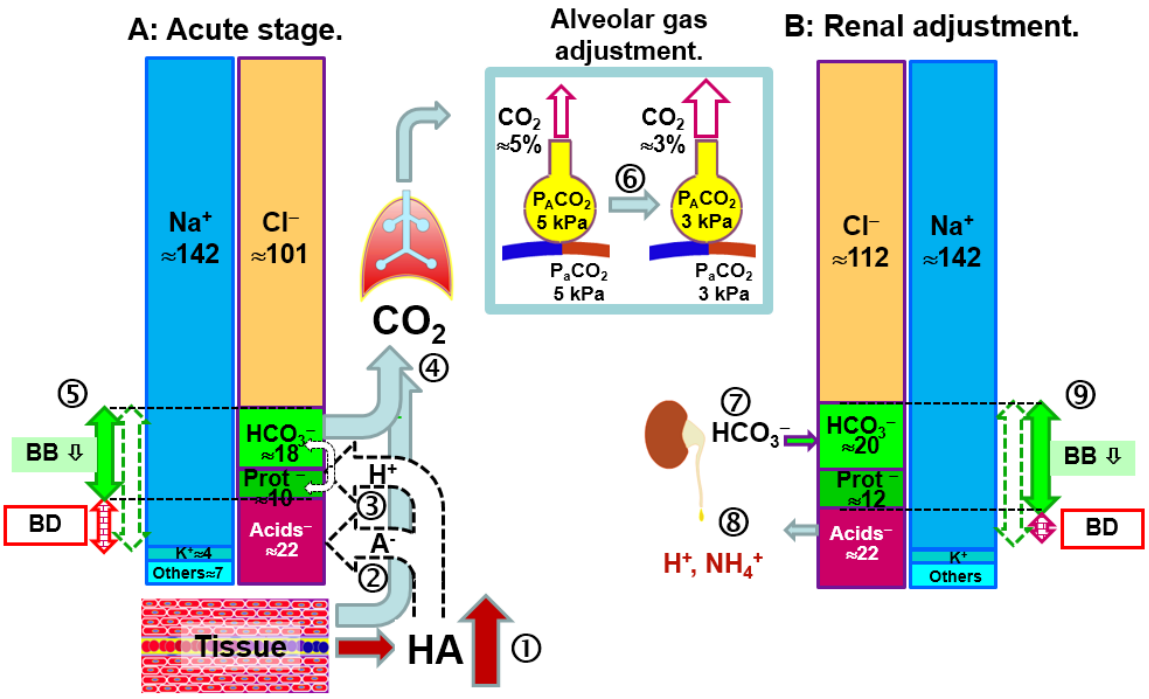


Figure 5-10. Metabolic acidosis due to increased levels of non-volatile acids.

A. Acute stage

When production of acids **HA** *(e.g. lactacidosis, ketoacidosis) proceeds at a rate in excess of the elimination capacity, the concentration of* **H^+** *ions and the acid's conjugate base (Acids$^-$ or* **A^-***) in the blood ① increases. The blood* **A^-** *increase ②, most of the increased* **H^+** *ions combine with* **prot$^-$** *or* **HCO_3^-** *③, reducing their concentration and increasing the generation of* **CO_2** *④. The ventilation increases in excess of than needed to eliminate the increased generation of* **CO_2***, and the blood* **PCO_2** *decreases. This consumes* **HCO_3^-** *ions and further reduces blood* **HCO_3^-** *levels. If ventilation cannot increase, the* **PCO_2** *in arterial blood rises and the fall in* **HCO_3^-** *levels is less than with a normal ventilatory response. The concentration of* **HCO_3^-** *and* **prot$^-$** *levels are both reduced ⑤, the BB decreases, establishing a Base Deficit (BD, = a negative Base Excess).*

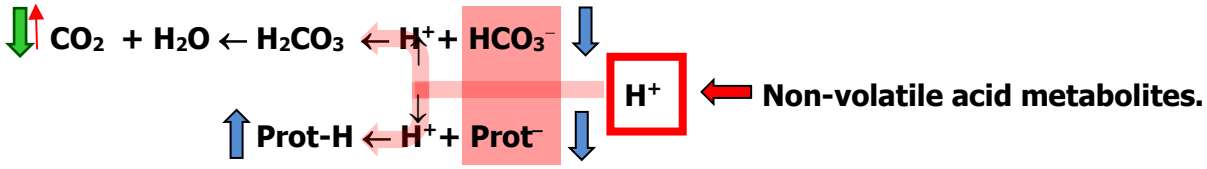
Pulmonary adaption

When **P_aCO_2** *decreases, the* **P_ACO_2** *also decrease; the number of* **CO_2** *molecules per ml in the expired gas ⑥ also decrease. Each ml of expired gas then contains a lower number of* **CO_2** *molecules and a new balance between produced and excreted* **CO_2** *establishes at a lower* **P_aCO_2** *level.*

B. Renal adaption

This is similar to that in acute respiratory acidosis: Renal tubuli cells respond to acidosis by increased reabsorption of **HCO_3^-** *⑦. Simultaneously, excretion of* **H^+** *ions increase ⑧ (see also fig 5-9);* **BB** *increases ⑨ and reduce the* **BD** *compared to levels in the acute phase. Such compensation is possible only when renal dysfunction or failure is not part of the etiology.*

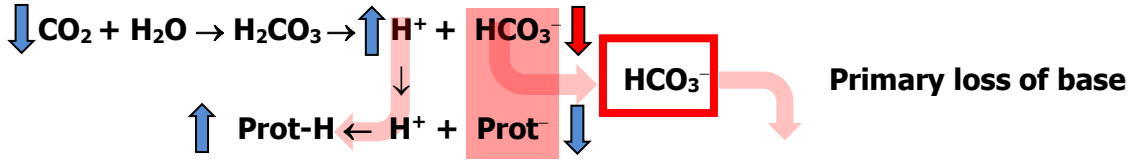
generated as the equation below shifts to the left. Despite the increased amount of CO_2 generated, the patient P_aCO_2 *does not increase*, but is reduced (*green arrow*) as the rise in blood H^+ stimulates the chemoreceptors and the ventilation increases *in excess of* that necessary to excrete the additional CO_2 generated by increased $[H^+]$ combining with bicarbonate.



Thus, with normal function of the lungs, chemoreceptors, and the respiratory center, most of the excess H^+ ions react with HCO_3^- and are eliminated from the body as CO_2. The end result is that the **P_aCO_2** in most patients is **reduced** during metabolic acidosis (fig. 5-10).

Metabolic acidosis due to loss of HCO_3^-: "Hyperchloremic acidosis".

A primary loss, or dilution, of a base in the extracellular fluid cause more CO_2 to be converted to H_2CO_3 and subsequently to HCO_3^-. According to the law of mass action, this rightward shift of the equation below also increases the $[H^+]$; most of them bind to protein buffers, whose concentration then decreases. Losing HCO_3^- through renal dysfunction or gastrointestinal loss (e.g. diarrhea with net bicarbonate loss) thus leads to acidosis and an increase in Cl^- relative to Na^+ ("hyperchloremic" acidosis), the increased chloride level is usually due to renal exchange of Cl^- for HCO_3^-.

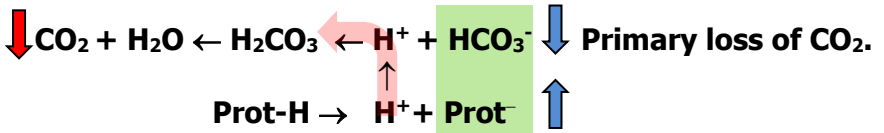


Excess administration of Cl^- (as infusions of NaCl) can also have this effect. According to the concept of Stewart, an increase of $[Cl^-]$ relative to $[Na^+]$ induces increased dissociation in water and thus increases $[H^+]$ in the body fluids (see below). As the concentration of both HCO_3^- and protein buffers decrease, **BB decreases** and a **base deficit** (or negative base excess, - BE) is created.

The two different causes of reduced buffer capacity in metabolic acidosis, i.e. *consumption* or *external loss* of base, can be identified by calculation of the **Anion Gap** (see below).

Acute Respiratory alkalosis.

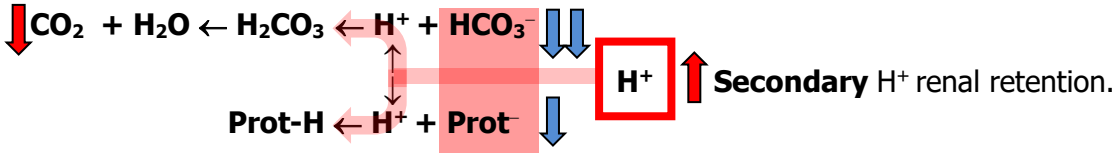
In primary respiratory alkalosis (most often caused by hyperventilation due to moderate hypoxemia or anxiety, but also by cerebral ischemia and damage), the CO_2 levels in the blood decrease. Increased amounts of H^+ and HCO_3^- ions also disappear with the excreted CO_2, at the same time a corresponding quantity of H^+ ions are released from Hb and albumin.



The increase in the quantity of protein$^-$ is *almost* directly proportional to the decrease in HCO_3^-, **BB remains constant,** and BE is unchanged (fig. 5-11).

Chronic respiratory alkalosis.

Chronic respiratory alkalosis is usually seen in connection with chronic non-critical hypoxia, often due to prolonged stays at high altitudes. Renal retention of H^+ ions and excretion of HCO_3^- can normalize the $[H^+]$; the prot$^-$ decreases and the HCO_3^- decreases further, reducing the total sum of buffers.



As **BB decreases,** a BD (or –BE) is established (fig. 5-11).

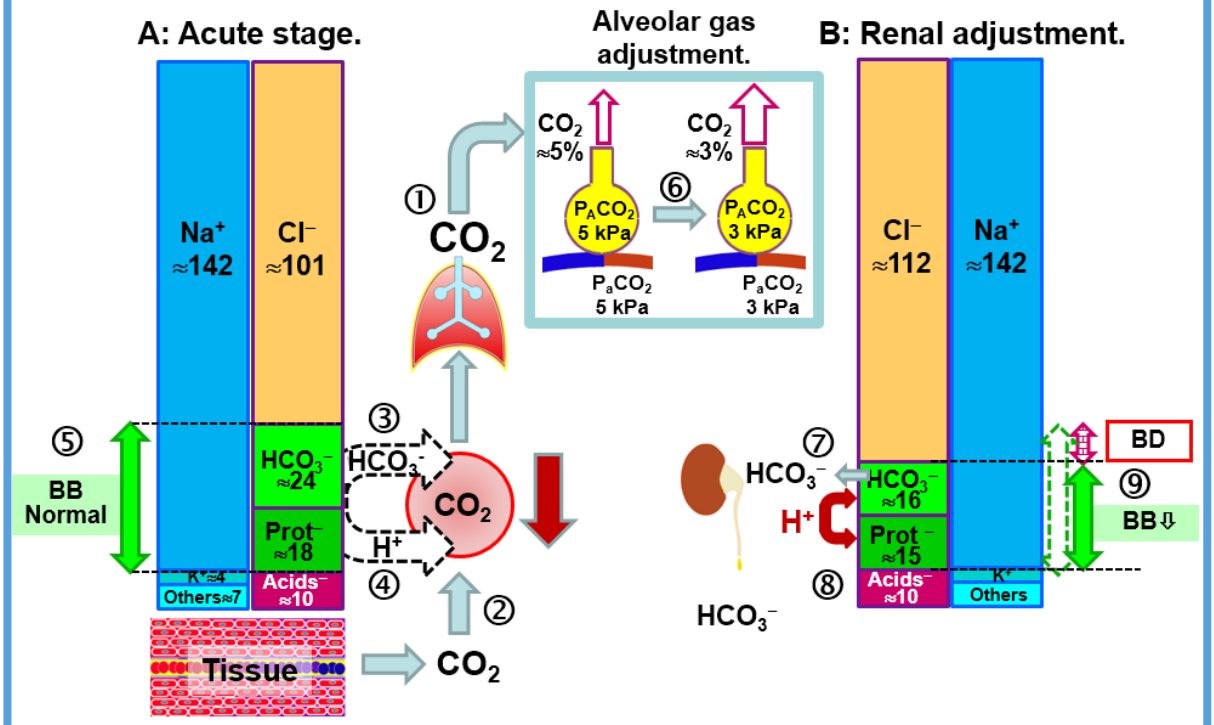


Figure 5-11. Respiratory alkalosis.

A. Acute stage.

When pulmonary excretion of **CO_2** ① *increases relative to that produced by tissues* ②, *blood* **CO_2** *levels (and thus* **PCO_2**) *decreases. The* **PCO_2** *decrease reduces the concentration of carbonic acid,* **H_2CO_3** *and* **HCO_3^-** ③. *Decreased* **H_2CO_3** *also decreases the number of* **H^+** *molecules, which then release* **H^+** *from* **prot** $^-$ ④. *As this increase is almost equal to the decrease in* **HCO_3^-**, *the* **BB** *is essentially unchanged* ⑤.

Pulmonary adaption

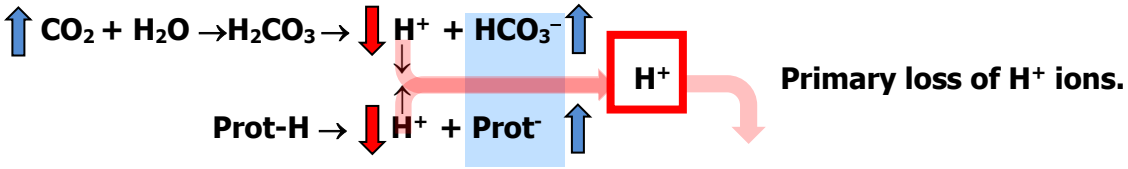
The **P_aCO_2** *reduction has the same effect on* **P_ACO_2** ⑥ *as described for metabolic acidosis (fig 5-10). Each ml of expired air contains less* **CO_2**, *the* **CO_2** *excretion becomes less efficient with falling* **P_ACO_2** *levels. A new balance between* **CO_2** *production and excretion is established at a lower* **P_aCO_2** *level.*

Renal adaption

Renal tubuli cells respond to alkalosis by increased excretion of **HCO_3^-** ⑦. *Simultaneously, reabsorption of* **H^+** *ions by the tubuli cells* ⑧ *increases, decreasing the net renal excretion of acid. If the blood* **H^+** *concentration normalizes, the* **prot**$^-$ *decreases. As* **HCO_3^-** *is also reduced,* **BB** *decreases and a* **BD** *(i.e. -BE) develops* ⑨.

Metabolic alkalosis. In primary metabolic alkalosis (increased loss of H^+ ions relative to HCO_3^- from the organism), ventilation will decrease to retain more H^+ in the form of CO_2 in the body. The quantity of HCO_3^- then increases along with the CO_2 increase; the deficit of H^+ ions causes more proteins to release H^+ and the quantity of negative charges on proteins will therefore

also increase.



The net result is an **increase in BB** and a positive BE (fig. 5-12).

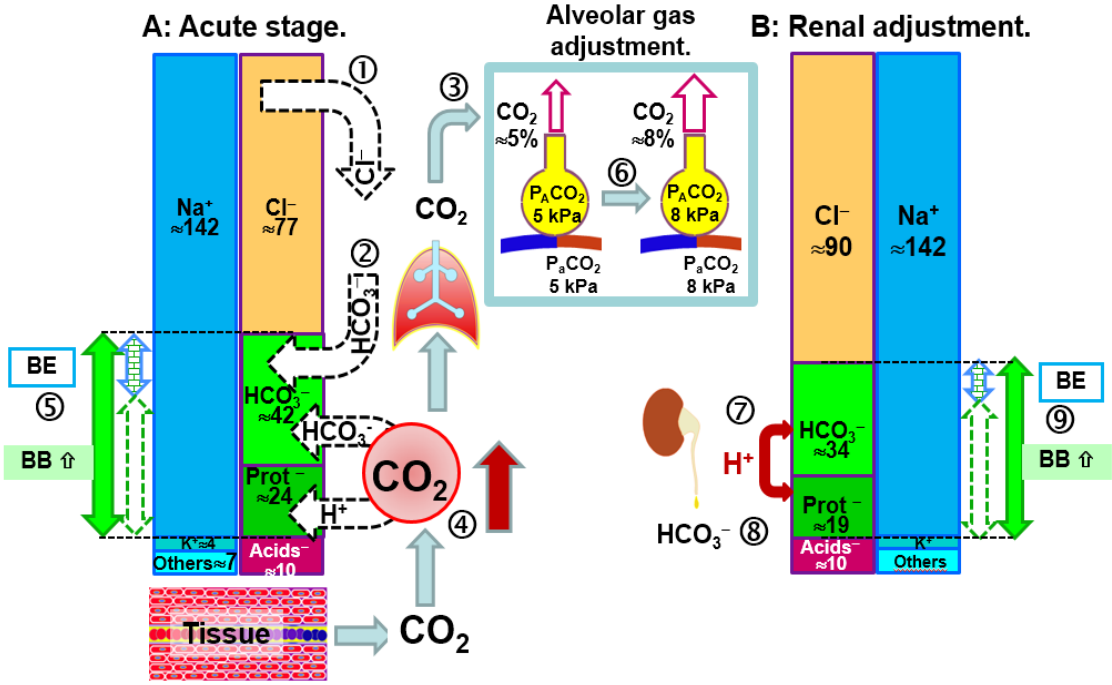


Figure 5-12. Metabolic alkalosis.
A nett loss of **H⁺** *ions from the organism in excess of their production, of non-respiratory etiology, is usually accompanied by a loss of* **Cl⁻** ① *and/or increased* **HCO_3^-** ②. *In response to alkalosis, the ventilation decreases* ③ *and blood* **CO_2** *and* **PCO_2** *increases* ④. *The* **H⁺** *decrease leads to augmented concentrations of both* **HCO_3^-** *and* **prot⁻** *levels, the* **BB** *increases with a positive* **BE** ⑤.
Pulmonary adaption.
The increased **P_aCO_2** *increases the* **P_ACO_2** ⑥ *in normally perfused and ventilated alveoli, increasing the number of* **CO_2** *molecules per ml expired air. This limits the* **CO_2** *accumulation in arterial blood and a new balance between* **CO_2** *production and elimination establishes at a higher* **PCO_2** *level.*
Renal adaption
Renal tubuli cells respond to alkalosis by increased excretion of HCO_3^- and reabsorption of **H⁺** *ions,* ⑦⑧⑨, *analogous to respiratory alkalosis (fig 9-11).*

The anion gap (AG) concept in metabolic acidosis.

A major weakness of the BB and -BE concept is that a calculated reduction of base capacity (i.e. –BE) does not discriminate well between conditions where ***i)*** the concentration of non-volatile acid increase and *consume part of the base capacity*, or ***ii)*** when *reductions in base capacity* are created by *external losses* of bicarbonate from the gastrointestinal system or the kidneys, *or* low protein (Hb, albumin) levels. In the latter, the mechanisms for generation and excretion of metabolic acids may be normal, the acidosis is created by an increased loss of base *or* a surplus of chloride

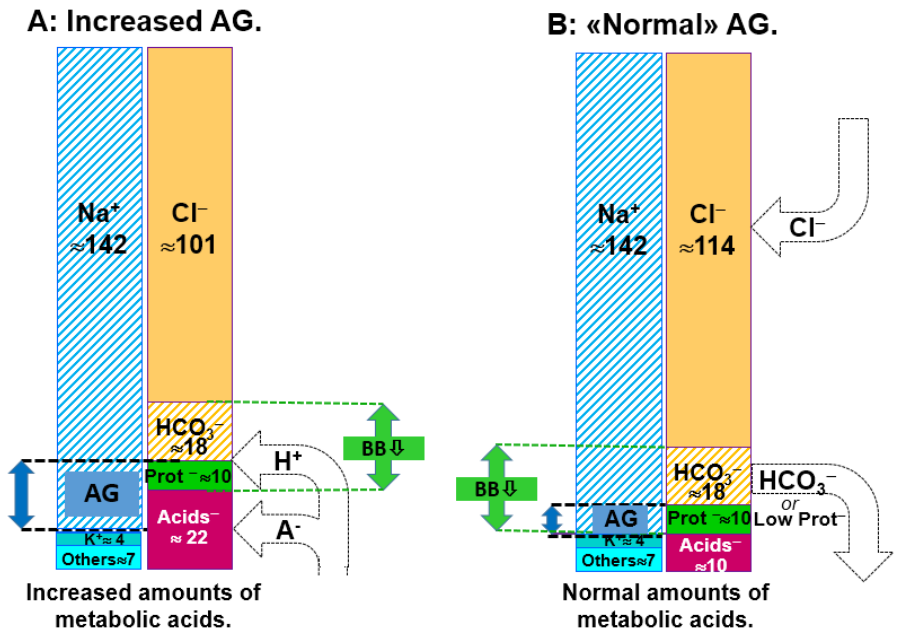


Figure 5-13. *The Anion Gap* (**AG**) *and comparison of metabolic acidosis due to* (**A**) *increased levels of acids⁻ and that due to* (**B**) *loss of HCO_3^- or Prot⁻ and/or increase in Cl^- .*
A. *Metabolic acidosis, as presented in fig 5-7A, not only reduce the BB, but also reduce the sum of (HCO_3^- + Cl^-) relative to the Na^+ concentration. The Anion Gap (AG) (see text) is therefore increased.*
B. *Even if the concentration of acids⁻ (i.e. the conjugate bases) remains normal, a metabolic acidosis may result from loss of buffers, especially HCO_3^-, or an acute increase in Cl^- relative to Na^+. The reduction in BB may be equal to that in* **A;** *if the Cl^- increase is of the same magnitude as the HCO_3^- decrease, the AG remains in the normal range.*

(see above). The AG concept was introduced during the 1970-ties (68, 69) to facilitate such discrimination**.**

The concept is based on the association between loss of buffer capacity *and* changes in the normal relationship between the concentration of major cations (*only* Na^+ *or* Na^+ + K^+) and the *sum* of the major anions (Cl^- plus HCO_3^-) (see below and fig. 5-13). Any state where both the BB *and* the difference between [Na^+] and [Cl^-] ions are reduced, should create suspicion about increased loss of HCO_3^- as a primary cause of metabolic acidosis.

Diagnostic use of the Anion Gap concept.

The anion gap (**AG**) is calculated as the difference between the concentration of Na^+ ions and the sum of Cl^- + HCO_3^- ions in the blood

$AG = [Na^+] - ([Cl^-] + [HCO_3^-])$

The mean normal value is 12 mmol/l (70) (see fig. 5-13); the range found in a population of normal persons is, however, wide. Some authors also include the K^+ concentration on the positive (cation) side

$AG = ([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$

leading to a lower normal value (67, 71).

In the *four most common* causes of acute metabolic acidosis (lactacidosis, ketoacidosis, renal and toxic agents acidosis), the HCO_3^- concentration is reduced after combining with excess H^+ ions during increased excretion of CO_2, and the *anion gap is increased.* These types of acidosis are therefore called *increased* or *high anion gap* metabolic acidosis (fig. 5-13).

In *less common* conditions, an *increase in Cl^- relative to Na^+* (e.g. *acutely*, as in rapid infusions of large quantities of NaCl, *chronically*, as in tubuli cell dysfunction), *or* a primary loss of bicarbonate (renal or gastrointestinal loss, where HCO_3^- is substituted by Cl^-) creates an acidosis but

do not cause a major change in the sum of Cl^- plus HCO_3^- ions. Metabolic acidosis due to such causes is therefore accompanied by an unchanged or reduced anion gap; it is often called metabolic acidosis with a *normal anion gap* or *non-gap metabolic acidosis* .

Limitations of the BB-BE and AG concepts in metabolic acidosis.

These calculations do not measure a change in non-volatile acid concentration directly but measure the *consequences* of such changes on buffers and electrolyte concentrations. Neither do they indicate which type of non-volatile acid that is responsible for the derangement. In addition, the equations used to calculate the BE varies between manufacturers of ABG analyzers and may include the actual concentration of Hb but not albumin.

The buffer effects of Hb and albumin are ignored in the original AG calculations; adjustments to take the albumin concentration has, however, been proposed. A low albumin concentration (e.g. liver failure, serious inflammatory disease) leads to a reduced buffer capacity, while certain types of proteins produced in myelomas have net negative charges (72, 73) and increase the total buffering capacity of the $proteins^-$. A correction factor, compensating for hypo-albuminemia as measured in blood, has been advo-cated by several authors (66, 74). A simplified formula for correction of protein buffer capacity due to hypoalbuminemia has been proposed; the modified albumin effect = 0.34 x (45 – patient albumin concentration) (75); others advocate a multiplication factor of 0.25 (76). In many se-verely ill patients (e.g. sepsis, major burns, massive trauma) the microvascular permeability is greatly increased, and much of the albumin normally kept within the intravascular space leaks out into the interstitial space (77, 78, 79). These interstitial albumin molecules still constitute part of the extracellular buffer system; the altered ratio between the albumin level in plasma and that unmeasured in the interstitial fluid makes the use of albumin correction based on plasma levels imprecise in such patients. As for bicarbonate, a change in levels is affected by the ability to mount an adequate ventiation response.

The advantage of both calculation methods above is that they are easy to understand for persons without advanced knowledge of chemistry and give a picture that is reasonably accurate in most acute acid-base disturbances. They have also been widely used by clinicians for several decades. The BB-BE method, when combined with, and supported by, a simple bedside calculation of the $Na^+ – Cl^-$ concentration difference ($\Delta (Na^+ – Cl^-)$), can detect and explain the majority of acid-base disturbances. In most acute clinical settings, an understanding of the principles (and limi-tations) of the "classical" Base Excess and Anion Gap methods will lead to correct conclusions.

The strong ion difference (SID) concept of Stewart.

A third method was introduced by Stewart (80, 81) to compensate for the limitations of the first two methods. None of them could properly explain why infusions of large amounts of NaCl (which reduce the difference between $[Na^+]$ and $[Cl^-]$ in the blood) could induce acute metabolic acidosis (82, 83). The Stewart principle focuses on the electroneutrality in plasma and is derived from the postulate that $[\mathbf{H^+}]$ changes in body fluids is *not* a direct result of generation of non-volatile acids *per se*, but is *secondary* to three independent factors: *i)* changes in the PCO_2, *ii)* the concentration of *conjugate bases of weak acids, and iii)* the *difference* between the concentration of *"strong"* (i.e. highly dissociated) *cations* ($Na^+ + K^+ + Ca^{++} + Mg^{++}$ etc.) *and anions* (Cl^- *plus* the conjugate base of highly dissociated metabolic acids like lactate, formate, oxalate, etc.), the **Strong Ion Difference**. The original calculations suggested by Stewart were complex; several modifications and simplifications have been proposed.

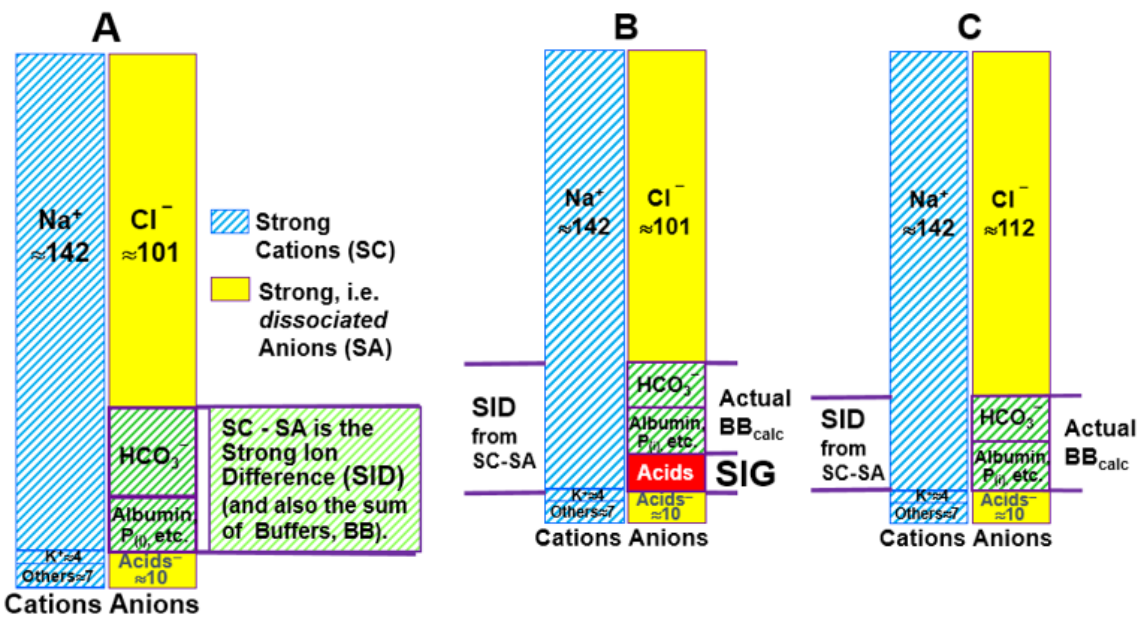


Figure 5-14: The Stewart method for classification of metabolic acid-base disturbances.

Simplified illustration of the strong ion difference and the BB according to Stewart, see text for details.

A. *In the normal state, the difference between strong cations and anions* (**SID_a**) *is almost equal to the* **BB** *(called* **SID_e** *by Stewart). His calculation of BB involves albumin and phosphate buffers ($P_{(i)}$) but not Hb.*

B. *Increased amounts of non-volatile acids reduce the BB. If Na^+ and Cl^- remains the same, the SID will be higher than the calculated BB. The difference between the results of the two calculations is the* ***Strong Ion Gap*** **(SIG)** *of Stewart (see text). This is comparable to the base deficit (BD or -BE).*

C. *If loss of base is the cause the acidosis, Cl^- increases by the same number of mEq/l as the decrease in BB ("hyperchloremic acidosis") and there is no difference (no "gap") between the calculated SID and the actual BB. See also anion gap, fig 5-13.*

The **strong ion difference**, as calculated from measured cations and anions (fig. 5-14) was termed **SID_a**, it is often simplified to calculating only the Na^+ - Cl^- difference. As the normal sum of *cations other than* **Na** (≈ 11 meq/l) and that of the normal conjugate bases (anions, A^-) from acids present in normal low concentrations (≈ 10 meq/l) is almost identical, the numerical value of the SID_a becomes *almost equal* to the **BB** in the "classical" concept of Singer, Hastings, and Siggaard-Andersen. The Stewart *method for calculation* of BB is, however, *different* from the classical; the actual concentration of base is calculated from plasma levels of bicarbonate, albumin (but not Hb, see above), and phosphate, corrected for the actual pH. The calculated sum of buffers was not called BB but **SID_e** by Stewart. The difference between the results of the two calculations, i.e. **SID_a** minus **SID_e** is called the **Strong Ion Gap (SIG)**. An *increased* SIG indicate an increase in unmeasured acids (in reality, their conjugate bases), analogous to the increased AG. A *reduced content of base* is accompanied by a change in both **SID_a** and **SID_e**, and there is no difference between the two, analogous to the non-gap, i.e. normal AG.

The Stewart method offers a somewhat increased diagnostic accuracy in complicated metabolic disturbances, especially those associated with pathological losses of H^+ or bicarbonate, and its use has been advocated by several authors (84, 85). It can also identify the presence of increases

in unmeasured anions in patients with an apparent normal acid-base status. It does, however, involve more parameters and calculations, and thus additional sources of error, several authors have suggested modifications to make the Stewart system easier to use in an everyday clinical context (74, 76, 86).

Whether the Stewart approach represents a better tool in daily clinical evaluation or during acute conditions is still uncertain (87, 88, 89, 90). Defining a condition with a close to normal pH as metabolic acidosis does not necessarily add to the bedside understanding of acid-base disturbances for clinicians (91, 92). Its usefulness in the world of acute and intensive care clinical medicine is debated (93, 94), many enthusiasts, however, embrace it.

COMMON CLINICAL CONDITIONS ASSOCIATED WITH ACID-BASE DERANGEMENTS: AN OVERVIEW

RESPIRATORY ACIDOSIS.

Failure of the lungs to excrete CO_2 at the same rate as its production by the tissue *without* increasing the P_AO_2 and thus the P_aO_2 (see fig 5-8) may be due to

- **Hypoventilation,** where the primary problem is a reduction of alveolar minute ventilation volumes below normal without a corresponding decrease in CO_2 production.
- **Increased alveolar dead space** *or* **a major local increase in the V/Q ratio** *or* **both**. The ventilation volumes *per se* are normal or increased, but a substantial part of the ventilated alveoli are hypo- or non-perfused and excrete little or no CO_2 (Part 4-2). The latter is the most common cause of increased P_aCO_2 in patients with chronic respiratory diseases.

T*o discriminate* between the two causes above, either the *i) ventilation volumes* (tidal- and minute ventilation) or ***ii)*** the *end-expiratory vs arterial* CO_2 must be known.

The options available to the organism for re-establishing the balance between CO_2 production and elimination during the latter condition (see also fig 4-19) are to

i) Increase the alveolar ventilation volumes further to maintain the excretion of CO_2 constant, preserving the PCO_2 (and thus also the P_aO_2) in alveolar gas and arterial blood at normal levels.

ii) Allow the concentration of CO_2 in the alveolar gas to increase. This augments the mass of CO_2 excreted by each milliliter of expired gas, but also increase P_aCO_2, and $[H^+]$ in arterial blood (see also fig. 5-8); the P_AO_2, and thus the P_aO_2, will then decrease (see below).

The latter strategy often involve P_aCO_2 increases to levels within 1.5 to 3 times normal values, this may lead to grave hypoxemia if breathing room air (Part 4-1). An extreme increase to almost 10 times normal values, with a P_aCO_2 of 50 kPa (375 mmHg), resulting in pH 6.60, has been reported to be compatible with a favorable outcome when the S_aO_2 was kept >90% by increasing the F_iO_2 (95), see also Part 4-4, pg. 286 and 296). If the increased P_aCO_2 become chronic, the acidosis may be diminished or disappear due to the renal compensatory mechanism while the increase in PCO_2 remains (see above and figs 5-8, 5-9).

Common conditions associated with acute or subacute (i.e. seconds to few days) **hypoventilation** (see Part 4-3 for details).

- *Acute obstructions of airways* (e.g. asthma, laryngitis, epiglottitis, and obstruction by foreign objects) are the most dramatic non-traumatic cause of hypoventilation. Such conditions often involve increased catecholamine levels and maximal effort of the respiratory muscles; the

resulting increase in muscle metabolism and the generation of CO_2 (respiratory acidosis) accelerate the development of hypoxia (lactacidosis) simultaneously. Severe mixed acidosis can occur within minutes, but severe hypoxemia develops faster.

- *Toxic effects of opiates or other drugs and agents* that interfere with the normal regulation of ventilation and/or neuro-muscular transmission in persons with normal or reduced CO_2 production. Respiratory acidosis develops within minutes to hours, severe hypoventilation may lead to grave hypoxemia and additional lactacidosis.
- Spontaneous *accumulation of fluid or air within the pleura*. Can be acute to subacute (minutes to hours to days).
- *Trauma* with injuries to the CNS or spinal cord, pneumo- and hemothorax, abdominal/thoracic wall damage, or surgical procedures that cause pain when breathing. Can occur within minutes to hours.
- Diseases that change the function of *the central nervous system (CNS) or peripheral nerves*, or inhibit normal neuro-muscular transmission. Usually subacute (days to weeks).

Common causes of increased alveolar dead space or major increase in the V/Q ratio.

- *Acute lung emboli* increase the alveolar dead space within seconds. This should theoretically cause a rise in PCO_2; due to concomitant hypoxemia and hyperventilation, the PCO_2 is often normal or reduced in the acute phase but may increase if respiratory muscle fatigue develops.
- *Pulmonary microembolism* (microthrombi, air bubbles, fat droplets) may also create areas of non-perfusion and increased alveolar dead space. Microtrombi are common in acute respiratory distress syndrome (ARDS); as hypoxemia is also common in such patients, hyperventilation often conceals the effect of changes in V/Q ratios on CO_2 excretion, keeping the PCO_2 normal.
- *Chronic inflammatory lung disease,* classified as chronic obstructive pulmonary disease, (COPD). This is a progressive condition which usually develops over several years and is commonly associated with increased V/Q ratios. Due to renal compensation, many such patients exhibit hypercapnia *without* acidosis.

Role of increased CO_2 production.

Increased production of CO_2 due to an augmented metabolic rate (muscular exertion, fever, increased catecholamine levels, malignant hyperthermia, hypermetabolism due to thyrotoxicosis, etc.) is normally well compensated by increased ventilation. It may, however, induce respiratory acidosis in persons with limited ability to do so. In patients already in respiratory failure with compensated hypercapnia, it may aggravate the imbalance between CO_2 production and excretion, increasing the alveolar and arterial CO_2 further until they stabilize at a new and higher level (see fig. 5-8) *or* lead to a requirement for ventilatory support in the rise in CO_2 becomes dangerous. **NB:** Increased P_aCO_2 with a neutral or alkalotic pH *may* represent a respiratory compensation for a metabolic alkalosis.

Sudden normalization of ventilation relative to CO_2 production.

If a chronically elevated PCO_2 is suddenly normalized due to start of manual or mechanical ventilation with increased ventilation volumes, the acid-base picture of arterial blood gases may be compatible with metabolic alkalosis (see below).

METABOLIC ACIDOSIS.

Acute metabolic acidosis is most frequently due to *accumulation* of the non-volatile acids *normally present* in the blood in low concentrations (i.e. the H^+ ions are generated during normal metabolic processes), *or* sometimes resulting from the metabolism of drugs or toxic substances (see above). This type of acidosis is characterized by *reduced BB*, i.e. a *base deficit or -BE*, and an *increased anion gap (AG).* If *loss of buffers* is the main cause of acidosis, the *AG* may be in the *normal range* (see above). A multitude of etiologies may induce such acidosis, including some rare congenital diseases; determining the underlying cause in acute settings without supplementary information can be a challenge. The normal response of the organism to metabolic acidosis is depicted in fig. 5-10.

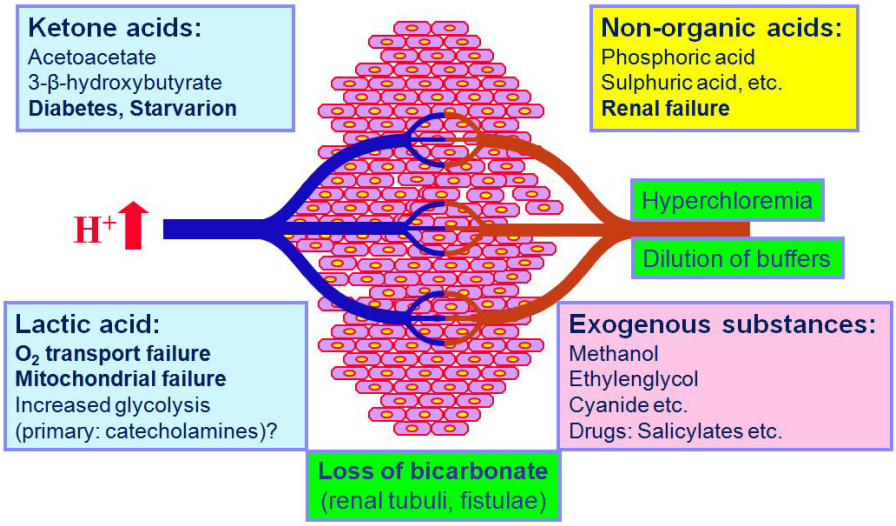


Figure 5-15. Common causes of metabolic acidosis.
Green colour indicate acidosis with normal anion gap (see text).

Figure 5-15 shows the most common conditions leading to metabolic acidosis. Acidosis caused by such processes are usually initiated by changes in intracellular metabolic processes, i.e. the intracellular acidosis is more accentuated than the extracellular one. In experimental acid-base research, the opposite is often the case. When acids are infused i.v. in experimental animals; the fluid surrounding tissues or cells are made more acid while the changes in intracellular pH lag behind. The H^+ gradients are thus opposite of the conditions usually found in clinical metabolic acidosis (except for the effect of lactacidosis resulting from severe muscular exertion, where all other organs are exposed to external, blood-borne acidosis); not all changes observed in acute experimental studies involving infusion of acids may be relevant to the pathophysiological processes in disease.

Metabolic acidosis due to increased levels of lactic acid (lactacidosis).

The most dramatic example of acute metabolic acidosis is the physiological *lactic acid accumulation* (lactacidosis) *during extreme exertion* in athletes; levels as high as 30 mmol/l may arise within less than an hour (96). Such levels are higher than those observed in most non-survivors during deep shock (97).

The most common causes of lactacidosis (see also Part 2-4) **are**

- *Oxygen deficiency* (e.g. shock, cardiac arrest, grave hypoxemia).
- *Heavy exertion* (physiological) or *severe convulsions/spasms* (e.g. grand mal attacks).
- *Metabolic changes* induced by infections, drugs, toxins, or genetic aberrations.
- *Severe liver failure* (acute or chronic disease or injuries).
- *Catecholamine stress* or agents acting as potent stimulators of the central nervous system.

Inborn mitochondrial dysfunction may in rare instances cause lactic acidosis (Part 2-4); lack of thiamine interferes with the normal function of the citric acid cycle and favors lactate production (98). *Drugs* (e.g. biguanides, drugs used in HIV and cancer therapy) may interfere with mitochondrial function and cause lactacidosis in some individuals (99, 100, 101); the lethal effect of some toxins (e.g. cyanide, hydrogen sulfide, formate) is a consequence of their ability to block normal mitochondrial function (52, 102, 103).

Metabolic acidosis due to increased levels of keto acids.

Keto acids are intermediate products in the metabolism of fats. If the intracellular concentrations of carbohydrates become insufficient (e.g. insulin deficiency, starvation), keto acids are not fully metabolized and the blood concentration increases. Generation of *keto acids* during diabetic ketoacidosis (104) develops much slower than lactacidosis, progression to severe acidosis usually takes several hours to days but may nevertheless result in life-threatening acidosis.

Ketoacidosis is most often caused by *poorly regulated diabetes*, but *alcoholism* (105) or *persistent fasting* or *starvation* (106) are also important causes. Of note is that starvation and alcoholism also may also lead to thiamine deficiency, which upon refeeding may induce lactacidosis (107) *in addition to* the previously established ketoacidosis.

In both lactacidosis and ketoacidosis, the levels of acid in the patient's blood may increase 10-fold or more compared to normal levels. An excess of both acids will be metabolized to CO_2 and water if the underlying cause of their increase is successfully treated; the acidosis diminishes rapidly when normal metabolic conditions are re-established. Lactate levels in healthy athletes fall to about 70% of the peak levels during the first 10 min after cessation of strenuous exercise and may be reduced to less than 50% of the peak value within a few hours in both athletes and patients (108). Ketoacidosis may normalize within 6-12 hours after the start of appropriate treatment (109).

Metabolic acidosis due to failure of renal acid elimination (renal acidosis).

The two most important acids (i.e. most often involved in serious disease) are **sulfuric** and **phosphoric acid,** these accumulate when renal failure becomes severe. Several other types of acids also contribute to acidosis in renal failure (110). Sulfate is liberated when certain amino acids (methionine, cysteine) are metabolized; phosphorus is especially plentiful in muscle (i.e. meat). In persons consuming a normal western diet, about 70% of the inorganic acids generated is sulfuric acid, its normal production is about 100 mmol per day, much lower than the other acids. This type of metabolic acidosis develops even more slowly; the development of severe acidosis due to renal insufficiency alone takes days. A diet that reduce the intake of sulfur and phosphor reduce the generation of these acids.

Mineralocorticoids (aldosterone and others) increase the excretion of H^+ ions by the kidneys during acidosis, subnormal levels of these hormones may attenuate the ability of normal kidneys to excrete the acid load derived from normal metabolism, and induce a metabolic acidosis (46).

Metabolic acidosis due to the presence of exogenous substances.

In addition to the etiologies above, metabolic acidosis may be caused by drugs, toxins, and various agents that may enter the organism through ingestion, infusion, or inhalation. Such substances may be ***i)*** acids *per se* (e.g. acetylsalicylic acid, amino acid solutions), ***ii)*** may add acids to the blood during their metabolism (e.g. methanol to formic acid, ethylene glycol to glycolic acid), or ***iii)*** create acidosis by interfering with normal metabolism (e.g. blocking of normal Hb

function, as for CO, *or* of the electron transport chain by cyanide and H_2S, biguanides, etc.). Substances that often cause severe metabolic acidosis in connection with *intoxication* are *methanol* (methyl alcohol), *ethylene glycol* (used as an antifreeze agent) (111), and *salicylates* (112). Intoxications with high doses of *paracetamol* (called *acetaminophen* in the USA) may inhibit mitochondrial function as well as damage liver cells to the extent that reduced clearance of lactic acid results in lactacidosis (113, 114). The development of severe acidosis varies with agents; those that interfere directly with the electron transport chain in the mitochondria may induce lactacidosis within seconds to minutes, while others take hours. In intoxications, the presence and degree of acidosis may vary considerably with different stages of the disease (53).

If metabolic acidosis occurs acutely in the absence of other reasonable causes, the possibility of exogenous/toxic substances should be investigated. In intoxications with toxic alcohols, analyzing the osmolar gap (see Apx) is a valuable additional tool (111).

Metabolic acidosis secondary to reductions of buffer capacity (normal AG acidosis).

A less common, but clinically relevant, cause of metabolic acidosis is a primary reduction in buffer capacity. This type is usually subacute and develops during many hours-days; pathological *loss of* HCO_3^- (e.g. renal tubular acidosis, pancreatic fistula, severe diarrhea) and/or increased *extracellular* Cl^- can lead to secondary changes in the regulation of H^+ ion concentration in the blood. The latter changes are usually associated with *infusions* of fluids with a high Cl^- content relative to Na^+ (83), the condition is therefore often called "hyperchloremic acidosis" (see also above). Also, *dilution* of the extracellular volume can alter the acid-base balance in an acid direction (see clinical pictures below); this mechanism is seen mainly after infusions of large volumes of i.v. fluids in connection with hemorrhage, trauma, and major surgery.

The relative importance of base dilution and infusions of excess chloride is debated, as are the exact mechanisms underlying this type of acidosis (115). The Stewart concept (see above) assumes, however, that a change in the relative concentrations of Na^+ and Cl^- also changes the dissociation of water molecules. Common to the above causes is that they, according to the law of mass action and the dissociation constant for carbonic acid (Part 5-1), create an acidosis *despite* a normal rate of H^+ ion production and preservation of normal H^+ ion elimination mechanisms (see also Anion Gap above).

RESPIRATORY ALKALOSIS.

Respiratory alkalosis is a disturbance where the rate of CO_2 excretion by the lungs exceeds its production in the initial phase, resulting in reduced P_aCO_2, $[H^+]$ and an alkalotic pH in the blood. After a while, a new equilibrium between elimination and production is reached, but at a lower P_aCO_2 level in both alveolar gas and blood which reduces the mass of CO_2 per milliliter of expired gas (fig. 5-11).

Acute respiratory alkalosis is usually a consequence of spontaneous hyperventilation (e.g. psychological mechanisms, early stage of sepsis (116), non-critical hypoxemia, not necessarily serious enough to cause lactacidosis (117), cerebral damage or ischemia (118), early stage of intoxica-tions with salicylates (112), etc. In mechanically ventilated patients, reduced CO_2 production (often caused by hypothermia) in the face of "normal" ventilator settings can lead to unintended low P_aCO_2 levels and respiratory alkalosis.

Chronic respiratory alkalosis is most common in individuals with normal lung function who resides at altitudes where moderate chronic hypoxemia is a source of continuous stimulation of the respiratory center (119). As moderate hypoxemia does not result in tissue hypoxia and lactacidosis, the pH stays in the alkalotic range although renal compensation (increased retention of H^+ ions, see below) will correct most of the initial change in pH if the renal function is normal.
NB. As reduced P_aCO_2 also may be a compensatory response to metabolic acidosis, *an alkalotic pH and a normal BB must be present* for the condition to be a true respiratory alkalosis.

METABOLIC ALKALOSIS.

Except for in iatrogenic over-treatment with base (e.g. $NaHCO_3$, THAM, and Tribonate®, see below), metabolic alkalosis is seldom acute but emerges in the course of many hours to days. It was previously found mostly in patients with loss of hydrochloric acid due to persistent vomiting (*hypochloremic alkalosis*), which could be accompanied by severe disturbances in the electrolyte status. Blood [Cl^-] as low as 38 mmol/l in the face of a close to normal [Na^+] have been observed in such a patient (120). In intensive care patients, continuous stomach tube drainage, long-term or aggressive diuretic therapy (121), and long term hemo-diafiltration with citrate as an anticoagulant (122) are frequent causes.

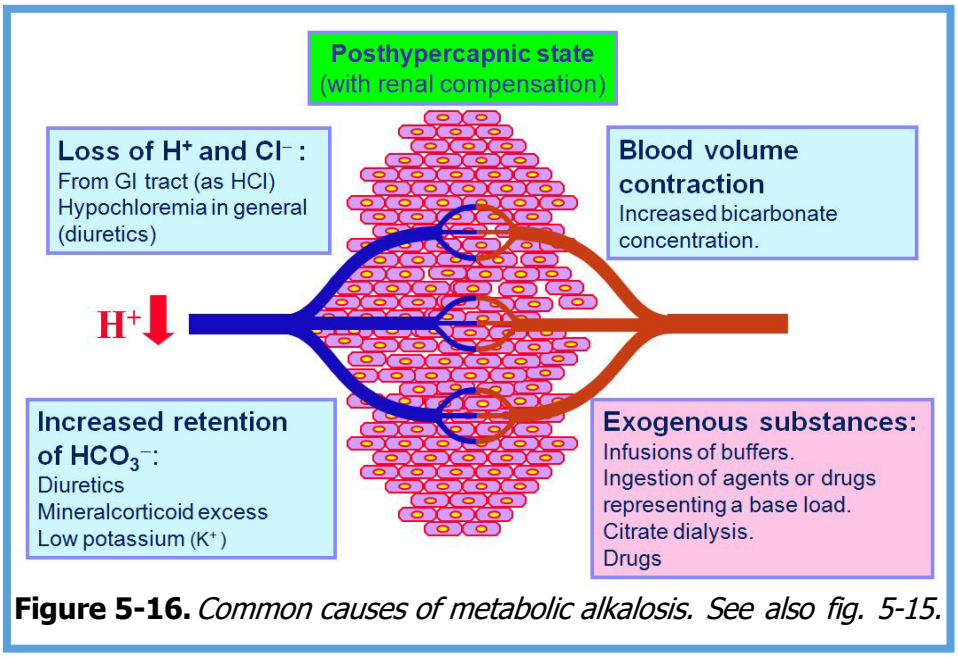


Figure 5-16. *Common causes of metabolic alkalosis. See also fig. 5-15.*

Metabolic alkalosis is often associated with *hypokalemia*. Increased levels of aldosterone and angiotensin II enhance the urinary excretion of H^+ and may lead to metabolic alkalosis (see above). Common causes of metabolic alkalosis are depicted in fig. 5-16, the response of the organism is shown in fig. 5-12.

Aggressive buffer treatment of metabolic acidosis that later resolves spontaneously with treatment (lactacidosis, ketoacidosis) may leave a surplus of buffer and thus a calculated BE in arterial blood, i.e. a metabolic alkalosis remains when the acids are metabolized.

NB: Reduced excretion of bicarbonate by the kidneys results in increased positive base excess (BE), and is often seen as a compensatory mechanism in chronic respiratory acidosis. This is not a metabolic alkalosis as long as blood pH is acidotic; it may, however, present as such if the CO_2 levels in a patient with chronically high PCO_2 are rapidly normalized (usually by ventilator treatment).

Sudden normalization of blood H^+ ion content.

If a reduced H^+ ion content that has been manifest for many hours/days is normalized within a few hours (e.g. infusions of arginine chloride or HCl, acute increases in lactate- or ketone production), and the renal compensation has been fully developed, the acid-base status may be relatively normal. In such acute generation of H^+ superimposed on a chronic alkalosis, low [Cl^-] levels relative to [Na^+], should, however, arouse suspicion. As ventilation may be decreased if the CNS fluid surrounding the central chemoreceptors is still alkalotic, the acid-base picture may resemble a respiratory acidosis with moderate renal compensation.

EFFECTS OF ACID-BASE DERANGEMENTS ON O_2 TRANSPORT

Oxygen supply to the tissues depends on the O_2 content of the arterial blood and the blood flow (Part 2-3). Acid-base derangements may interfere with almost all aspects of blood and tissue oxygenation. Unfortunately, once such negative effects on the DO_2 are established, correction of the derangements does not seem to reverse them, at least not on a short-term basis (see Therapy below). The changes induced by shifts of the HbO_2 dissociation curve after blood storage are, however, readily reversible and may improve O_2 supply conditions (123).

Effects on arterial blood O_2 content (C_aO_2) and tissue oxygenation.

The major determinants of C_aO_2 are S_aO_2 and Hb, with P_aO_2 playing a minor role (Part 2-3). Extreme acidosis causes a substantial rightward shift of the HbO_2 dissociation curve; at normal P_aO_2 values, the S_aO_2, and thus the O_2 content of the arterial blood, may be reduced by more than 20% (see fig 2-20). If the pulmonary function is also compromised and the P_aO_2 is low, a substantial rightward shift of the HbO_2 dissociation curve can reduce the O_2 content of the blood to approximately 50% of that at normal pH (see fig 4-12 and ref 48). After massive transfusions with stored blood, however, acidosis may in part reverse the leftward HbO_2 dissociation curve caused by low concentrations of 2,3-DPG in such blood (123).

On the other hand, alkalosis causes a leftward shift of the HbO_2 dissociation curve, which increases the S_aO_2 relative to P_aO_2. This increases the arterial O_2 content in states where the major oxygenation problem is due to severe pulmonary failure*or* when breathing a gas with a reduced O_2 content leads to low P_aO_2 values. This advantage is diminished if the leftward shift persists in the tissue microcirculation; tissue hypoxia and/or increased PCO_2 may, however, acidify the capillary blood in the microcirculation and cause a local rightward HbO_2 curve shift with increased O_2 release to tissues. The assumption of a net beneficial effect of a leftward HbO_2 curve shift when the PO_2 is low is supported by the physiological leftward HbO_2 curve shift (due to HbF) during birth when the baby's PO_2 often is extremely low (see below). Besides, individuals born with Hb variants that cause substantial leftward shifts in the HbO_2 dissociation curve manage fairly well; marked alkalosis due to hypoxic hyperventilation in mountain climbers on Mount Everest is also well tolerated (Part 4-2).

Severe acidosis also interferes with the coagulation system (4, 124), especially when combined with hypothermia (125, 126). Coagulation dysfunction aggravates bleeding and leads to severe anemia in traumatized patients and others with major hemorrhages. The triad of hypoxia, hypothermia, and acidosis is associated with coagulopathy and increased bleeding; coagulopathy is an independent risk factor for poor outcomes (127). Unfortunately, rapid normalization of pH after induction of acidosis does not seem to normalize the coagulation in *in vitro* studies (125).

Effects on the circulation.

Severe acidosis (pH < 7.15-7.10) has a negative inotropic effect on the myocardium and may decrease the cardiac output (128, 129). In moderate acidosis, this effect may be masked by a simultaneous increase in catecholamine activity; acidosis also accentuates the cardio depressive effect of simultaneous hypoxemia (130). In addition, acidosis aggravates the risk of cardiac arrhythmias due to a hypoxia-induced increase in catecholamines, as shown in experimental animals (131, 132).

Severe acidosis also impairs the vascular reactivity to both vasoconstrictors and vasodilators (133). This may lead to dysfunction or the mechanisms active in the normal distribution of blood flow between tissues and organs.

Alkalosis (with pH ≥ 7.60) also blunts the inotropic response of the heart (134, 135); in addition, it can also reduce coronary perfusion (136, 137). Acute decrease of PCO_2 causes vasoconstriction of cerebral vessels and may cause cerebral hypoperfusion (138). Also, the low pCO_2 of acute respiratory alkalosis increases neuromuscular irritability and precipitates convulsions, which again may reduce local muscular flow. Chronic alkalosis (due to hyperventilation at high elevations) seems, on the other hand, to be well tolerated.

5-4. INTERPRETATION OF LABORATORY ANALYSES; DIAGNOSIS AND TREATMENT OF ACID-BASE DERANGEMENTS

INTRODUCTION

For clinicians faced with an acutely ill patient with severe acidosis, an important question is whether the increase in $[H^+]$ is a result of ***i)*** *respiratory insufficiency*, ***ii)*** *changes in the balance between production and excretion of endogenous non-volatile acids,* ***iii)*** *loss of buffers and/or electrolytes*, or the rarer ***iv)*** *toxic agents or side effects of legal drugs* – or *any combination* of these. Various *renal diseases* and *congenital dysfunction of tubuli cell functions* are also important causes of acid-base derangements (139); these are seldom acute.

Respiratory insufficiency can, in most patients, be easily diagnosed by the parameters included in arterial blood gas (ABG) analysis alone (see below); the primary interventions for gaining control over the acidosis consist of antidotes (in intoxications with opiates or other agents) *or* ventilation support until the underlying cause can be corrected (if possible).

Identification of the cause of **metabolic derangements** may require additional laboratory data, and demands a broader understanding of acid-base regulation for correct interpretation and treatment.

Practitioners with different backgrounds may focus on different aspects of acid-base derangement. Those with a background in anesthesia, trauma care, emergency medicine, and acute medicine in general often focus on problems arising from acute respiratory and circulatory failure plus acute changes in metabolic processes, where life-threatening acidosis can develop within minutes to hours. Initial diagnosis based on the calculation of BB and AG, supplemented by calculation of the $[Na^+]$ - $[Cl^-]$ difference, has traditionally been the common approach among medical personnel caring for such patients.

Those with a primary interest in renal diseases and failure, or in physiological chemistry, tend to focus on more complex problems with a different timeline; an imbalance between the generation and excretion of non-volatile acid metabolites dependent on renal excretion may exist for days before the derangement becomes a serious threat to the organism. The limitations of BB, AG, and (Na^+ - Cl^-) calculations may be more important in chronic conditions; many of the supporters of the Stewart approach have such backgrounds.

The suggestions for interpretation below are colored by the author's background in anesthesia and acute and intensive care medicine. Figure 5-17 below shows the expected timelines for development of clinically important acidosis in various conditions. Intoxication with agents that blocks the activity of the electron transport chain (e.g. cyanide) may, however, cause acidosis within seconds to minutes but may also result in death *before* lactacidosis becomes obvious.

USING CHANGES IN BUFFER AND ELECTROLYTE CONCENTRATIONS IN ARTERIAL BLOOD TO DIAGNOSE CAUSES OF ACIDOSIS AND ALKALOSIS

Imbalances between H^+ ion production and elimination: General considerations.

The pH of intracellular fluid is, under normal circumstances, somewhat lower than in the blood, usually measured in the range of 7.00 – 7.40 (140); intracellular erythrocyte pH (i.e. the pH in

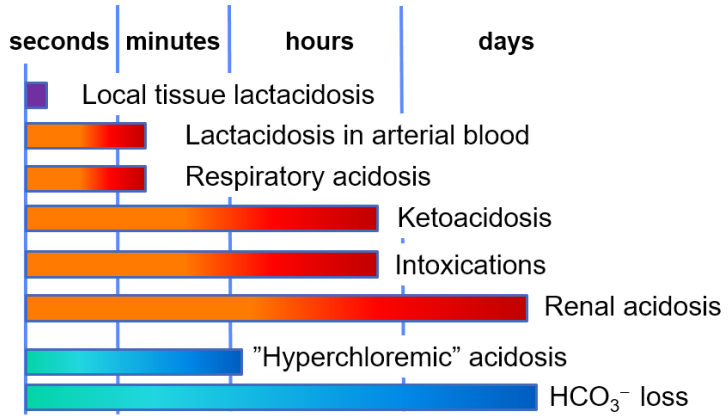


Figure 5-17. *Timelines for expected development of serious acidosis in the blood - "worst-case" scenarios. Acidosis after intoxication with cyanide etc. may, however, start within seconds.*

the fluid surrounding the Hb molecules) is in the range 7.15-7.25 (141). An increase in intracellular $[H^+]$ and the conjugate base of acids adds to their cell-to-capillary concentration gradient; acidosis is first detected in the venous blood draining the affected tissue. If the increase surpasses the organism's capacity for elimination, increased $[H^+]$ and levels of the conjugate base of acids are subsequently found also in arterial blood.

Direct measurement of acid-base status and oxygen parameters inside cells and in tissues would give a precise and early view of an H^+ imbalance. Techniques for such measurements exist but are presently not suitable for use in acutely ill patients at the bedside. Even if the acid-base changes found in the arterial blood of patients with an acute $[H^+]$ imbalance represent an imprecise reflection of intracellular derangements, such blood samples are usually easy to obtain; any major deviation in the ratio between H^+ ion generation and elimination will, within a few minutes, be reflected first in venous blood and then in arterial blood. Acid-base conditions in the interstitial fluid can be considered more representative of cellular conditions than those in the arterial blood, consequently, recalculation of the result found in a blood sample to the assumed mean value for the whole ECV space, "standardization" of base excess are often used (see below).

Blood gas analyzers and reporting of values.

The **core** *measurements* special to blood gas analyzers (often called ABG – arterial blood gas analyzers) are the measurement of **pH** and the **partial pressures of O_2** *and* **CO_2** in samples of blood. The most common source of blood samples for analysis is arterial blood. Unless otherwise specified, the values discussed below refer to arterial samples.

Modern analyzers are often also equipped with co-oximeters, which measure the SO_2 in the samples by direct oximetry instead of relying on calculations based on other parameters (see below). Other important acid-base parameters, like **bicarbonate (HCO_3^-), buffer base (BB)** *and* **base excess (BE),** are *calculated values* based on the pH, PCO_2, and hemoglobin values. Their relative impact in empirical algorithms may differ between various brands of ABG analyzers. Analysis of blood sampled from various non-arterial sites (see below and fig. 5-19) may supply additional information about the state of circulation.

As the analysis technology becomes more sophisticated, modern ABG analyzers often includes analyses of several additional parameters. Many of these, e.g. lactate (which are representative of the lactic acid concentration), albumin, Hb, Na^+, and Cl^-, are helpful for the interpretation of acid-base disturbance etiologies, especially some types of metabolic acidosis and conditions during acute-on-chronic disturbances. Taken together, these parameters contain most of the information necessary for the evaluation of the acid-base status in a blood sample and may offer clues to the etiology of disturbance (see below).

Common symbols and units in blood gas reporting (See also Apx).

There is no unanimous agreement about symbols and abbreviations used in blood gas analysis reports (142, 143). A list of the most commonly used symbols is shown below.

pH: The negative value of the logarithm denoting the concentration of H^+ ions. A pH = 7.40 equals a [H^+] of 40 nanomol/l (nmol/l), see Table 5-1 for other pH – [H^+] relationships.

PO_2: **The partial gas pressure of O_2** in the blood sample, also written as pO_2, *pO_2*, *PO_2*.

PCO_2: **The partial gas pressure of CO_2** in the blood sample, also written as pCO_2, *pCO_2*, *PCO_2*.

Pressures of the dissolved PO_2 and PCO_2 are usually given as absolute pressures, i.e. as a fraction of the ambient pressure. In Europe and many other countries, they are given in **kPa**; in the USA, the units are still given in **mmHg** (or Torr): 1 kPa = 7.5 mmHg (or Torr).

Identification of sampling site: Arterial samples are denoted **a** (e.g. P_aO_2, S_aO_2), **venous** samples **v** (e.g. P_VO_2, S_VO_2). Blood samples from all arteries are identical, but distinctions must be made between samples from *peripheral* veins, *central* veins, and *mixed venous* blood (see below). **Capillary** samples are usually denoted **c** (e.g. P_cO_2, S_cO_2).

Bicarbonate: The **HCO_3^-** concentration is a *calculated value* utilizing the measured [H^+[and PCO_2 (see Part 5-1) and given in millimol/l (mmol/l). The value corresponding to the actual PCO_2 of the patient is called the *actual bicarbonate* (**aHCO_3^-**); recalculation of the value to what it would be if PCO_2 was normal gives the *standard bicarbonate* (**sHCO_3^-**).

Buffer base (BB): The **total buffer capacity** (HCO_3^-, Hb, and albumin) of the extracellular fluid space and given in millimol/l (mmol/l). It is a *calculated value*, the *equations* used for calculation varies as to whether the actual Hb and albumin levels are included.

Base excess (BE): A **positive value** indicates that the *calculated BB* is higher than normal, and indicates an *increased* concentration of buffers (i.e. a reduced [H^+]). A *negative value* **(-BE)** - also called **BD** (base deficit) - indicates *a reduced* concentration of buffers. It can be presented as calculated for blood (**B**EB) or extracellular fluid (BE_{ecf} *or* **S**BE).

SO_2, also presented as sO_2 or O_2sat, is a measure of **the number of Hb molecules that are saturated with O_2** as a percentage of the total **number of Hb molecules.** It may also be reported as the fraction of Hb molecules saturated with O_2: **$FHbO_2$** *or* **FO_2Hb**. $FHbO_2$ = 0.9 equals SO_2 = 90%. Blood with a high O_2 content is bright red; blood from patients with CO intoxication or severe anemia may also look bright red despite a low S_aO_2. Blood with a normal Hb and low O_2 content is very dark blue to black.

HHb (or FHHb) is the percentage or fraction, respectively, of **deoxygenated Hb**.

COHb (or FCOHb) (carboxyhemoglobin) is the percentage or fraction, respectively, of **Hb molecules where carbon monoxide** (CO) **occupies the O_2 binding sites**. As small amounts of CO is produced endogenously, the normal value is 1-2%, higher in smokers.

MetHb (or FMetHb) (methemoglobin) is the percentage or fraction, respectively, of **Hb** molecules **with Fe^{+++}** instead of **Fe^{++}**. **MetHb** is unable to bind O_2, small amounts are produced endogenously and the normal value is 0.5-1.5%. If the MetHb is high, the blood is brownish– *and does not change color upon oxygenation*.

SulfHb or SHb (or FSulfHb/FSHb (sulfhemoglobin)) is the percentage or fraction, respectively, of **Hb molecules bound to sulfur ions. SulfHb** is unable to bind O_2, it is not present in normal blood. Blood with a high SulfHb has a greenish tinge– *and does not change color upon oxygenation*. This condition is rarely encountered.

Interpretation of arterial blood gases in acute conditions.

By convention, the categorization of acid-base derangements is based on the analysis of arterial, or arterialized (capillary blood from well-perfused skin), samples. Except for conditions occurring during *heavy muscular exertion* and states of *severely reduced blood flow* (see Part 3-3, shock states), the difference in pH between arterial and venous blood in well-circulated individuals is modest and of little clinical significance. A normal pH does*not* exclude a change in the acid-base or buffer balance, as both renal adjustment of H^+ excretion in chronic respiratory failure as well as acute-on-chronic conditions may result in a normal pH.

When it comes to O_2 and CO_2, however, samples from arterial and mixed venous blood contain different types of information. The main advantage of *arterial samples* is that *i)* the P_aO_2, relative to the calculated P_AO_2, reflects the efficiency of pulmonary O_2 gas exchange, *and ii)* the P_aCO_2 reflects whether the pulmonary excretion of CO_2 matches its generation in the tissues. The main advantage of samples of *mixed venous samples* are *iii)* the P_VO_2 and S_VO_2, when compared to the arterial O_2 content, reflects the relationship between the O_2 supply and consumption of the organism (the $DO_2/\dot{V}O_2$ ratio), *and iv)* the P_VCO_2, compared to the P_aCO_2, reflects whether the microcirculatory flow matches the metabolic activity of the tissues. In severely ill patients, supplementing arterial blood gas analysis with analysis of blood taken from a major central vein or the pulmonary artery may give additional information. When interpreted correctly, it may be valuable both for diagnosis, estimation of the gravity of the condition and choice of interventions.

In some situations,*e.g.* during heavy exertion but*before* the lactic acid (anaerobic) threshold of the muscles is reached, both pH and PCO_2 in mixed venous samples may show values similar to those seen in a substantial respiratory acidosis, while arterial samples show an acid-base status close to normal (144).

A schematic overview of expected changes in arterial blood gases in various acute and compensated disturbances, is presented below and in table 5–4. In more complex disturbances, however, the findings may deviate somewhat from those outlined in the table. Smaller deviations from the values given as normal for the various parameters may represent individual variations and do not necessarily indicate imbalance or disease. The simple rule-of-thumb interpretations below refer to **acute-subacute disturbances** *before* renal compensation is achieved, and may not be representative of compensated states or acute-on-chronic conditions.

pH (normal range 7.35 – 7.45).

Is there an **acidosis** (pH < 7.35,*high* **[H^+]**) or **alkalosis** (pH > 7.35,*low* **[H^+]**)?

- If **acidosis**: a significantly **increased PCO_2** indicates a respiratory etiology (expected **BE** between -3 mmol/l and +3 mmol/l) *or* a mixed respiratory-metabolic disturbance (expected **BE** < - 3 mmol/l), a significantly **decreased PCO_2** indicates a respiratory compensation for metabolic acidosis (expected **BE** < - 3 mmol/l).
- If **alkalosis**: a significantly **decreased PCO_2** indicates a respiratory etiology (hyperventilation, expected **BE** between -3 mmol/l and +3 mmol/l), a significantly **increased PCO_2** indicates a respiratory compensation of a metabolic alkalosis (expected **BE** > + 3 mmol/l).
- If pH is within **normal range**: are **PCO_2, BE** and the [**Na^+- Cl^-**] gap all **close to normal**? If significant deviations, a normal pH may be a result of a pulmonary/renal compensation of an initial acid-base disturbance or an acute-on-chronic derangement.

PCO_2 (normal mean value 5.3 kPa (40 mmHg)

- **Low values** ($P_aCO_2 \leq$ 4.7 kPa *or* 35 mmHg): Usually a result of **hyperventilation**, either **primary** (e.g. hypoxic, psychogenic, cerebral acidosis, etc. with expected pH > 7.45) *or a* respiratory **compensation for metabolic acidosis** with expected pH < 7.35**.** May also be caused by normal ventilation volumes during controlled ventilation in **hypothermic** patients.
- **High values** ($P_aCO_2 \geq$ 5.9 kPa or 45 mmHg): May be caused by **hypoventilation,** i.e. *low ventilation volumes* (*primary* hypoventilation due to lung disease, central nervous depression, mechanical factors, etc. with expected pH < 7.35) *or* be a **compensation for metabolic alkalosis,** with expected pH > 7.45**.** If *ventilation volumes are normal or increased*, **increased V/Q or alveolar dead space**, *or* significantly **increased metabolic rate** (see below) are probable causes.
- The **arterio-venous PCO_2 difference** (*P_aCO_2* supplemented with *P_vCO_2* from *central venous or mixed venous blood)* indicates whether the blood flow through the tissues matches their metabolic activity (see below).

NB: The P_aCO_2 must always be interpreted in the light of the ventilation pattern and volume, adjusted for the assumed CO_2 production (shivering, muscle contractions, thyrotoxicosis, catecholamine stress, etc. *increased* CO_2 production). Raised temperature increases O_2 consumption and thus also CO_2 production (see Part 2-3).

HCO_3^- (bicarbonate – normal mean value 24-26 mmol/l))

- If increased *and* acidosis: Respiratory acidosis.
- If increased *and* alkalosis: Metabolic alkalosis.
- If decreased *and* acidosis: Metabolic acidosis.
- If decreased *and* alkalosis: Respiratory alkalosis.

BE (base excess - normal value ± 0-3 mmol/l).

BE is an increase in the sum of buffers, compared to normal values (buffer base - BB). A base deficit (**BD**), i.e. a decrease in the sum of buffers, is often reported as a negative BE (**-BE**).

- If BE is normal *and* acidosis *and* P_aCO_2 increased: Acute respiratory acidosis.
- If BE is normal *and* alkalosis *and* P_aCO_2 decreased: Acute respiratory alkalosis.
- If BE is < –3 mmol/l *and* acidosis *and* P_aCO_2 decreased: Metabolic acidosis with respiratory compensation. It may be due to *either **i)*** consumption of buffers (i.e. buffering of increased $[H^+]$) from increased levels of acids), ***ii)*** reduced levels of Hb or albumin, *or **iii)*** increased external loss of **HCO_3^-**.
- If BE is < –3 mmol/l *and* acidosis *and* P_aCO_2 normal/increased: Metabolic acidosis without respiratory compensation *or* combined respiratory/metabolic acidosis.
- If BE is > +3 mmol/l *and* acidosis (or normal pH) *and* P_aCO_2 increased: Respiratory acidosis with metabolic compensation (chronic respiratory acidosis).
- If BE is > +3 mmol/l *and* alkalosis *and* P_aCO_2 increased: Metabolic alkalosis with respiratory compensation.
- If BE is > +3 mmol/l *and* alkalosis *and* P_aCO_2 normal: Metabolic alkalosis as compensation for previously chronically increased P_aCO_2 (may result from mechanical ventilation of COPD patients).

Anion gap (AG) (normal value approximately 12-16 mmol/l – see above). **NB:** Calculations meaningful only in metabolic acidosis, i.e. when the BE is negative.

- If $[Na^+ - (Cl^- + HCO_3^-)] \geq 14$ mmol/l *and* acidosis: Metabolic acidosis due to primary increase in acids.
- If $[Na^+ - (Cl^- + HCO_3^-)] \approx 14$ mmol/l *and* acidosis: Metabolic acidosis due to *i)* **Cl^-surplus** *or ii)* loss of HCO_3^- *or* both.

If K^+ is included in the equation, the "normal" gap value will increase with the value of K^+.

Strong ion gap (SIG) (normal value ± 0). **NB:** Calculations meaningful only in metabolic acidosis, i.e. when the BE is negative.

- If increased: Metabolic acidosis due to primary increase in non-volatile acids.
- If decreased: Metabolic acidosis due to reduction/loss of base.

$[Na^+]$ minus $[Cl^-]$ (Normal value ≈ 40 mmol/l)

- Reduced $[Na^+]$ - $[Cl^-]$ difference in the blood is seen in acidosis arising as a result of increased loss of base ("normal AG acidosis") or overload of chloride (usually after infusions of substantial amounts of saline (NaCl) solutions).
- Increased $[Na^+]$ - $[Cl^-]$ difference in the blood is common in metabolic alkalosis due to uncompensated loss of chloride (often due to profuse vomiting).

PO_2 (normal mean value at sea level is 13.3 kPa (100 mmHg), reduced levels in the elderly).

- The arterial PO_2 (P_aO_2) reflects the state of gas exchange in the lungs; in normal lungs, it is close to the calculated P_AO_2 (see also fig. 5-19). A correct interpretation of changes in P_aO_2 requires *comparison* with the P_AO_2 calculated by the alveolar gas equation Part 4-1). The P_AO_2 cannot be reliably calculated in patients with supplemental O_2 via nasal catheters or open face masks (Part 4-4).
- The arterial PO_2 is, *per se,* a poor indicator of the arterial blood O_2 content (C_aO_2), as changes in both pH and temperature may have a substantial impact on S_aO_2, see also below.
- A P_aO_2 value substantially higher than the assumed or calculated P_AO_2 may be found when samples are taken from hypothermic patients (where the solubility of O_2 is increased) and analyzed at 37°C without correction for the temperature difference. See below for temperature correction.

NB: In patients with anomalies of the heart and/or great vessels, resulting in an anatomical right-to-left shunt, P_aO_2 values may be substantially reduced despite normal lung function.

S_aO_2 (normal mean value when PO_2 is 13.3 kPa is 97.5%).

NB: Depending on the type of ABG analyzer, reported values of **SO_2** may represent either *calculated values* or be a result of *direct measurements* by a co-oximeter. The former may be erroneous in patients with CO intoxications, variant Hb molecules, significant changes in intra-erythrocyte 2,3-DPG levels, and other conditions associated with HbO_2 curve shifts (Part 2-3).

- The S_aO_2, together with the **Hb**, determines **the O_2 content of arterial blood** in patients with normal Hb function (dissolved O_2 represents *only* 1-2% of all arterial O_2).
- S_aO_2 is, *per se*, a poor indicator of pulmonary gas exchange.
- S_aO_2 (calculated) may be overestimated in patients with CO intoxication, methemoglobinemia, and dysfunctional Hb (see Part 2-3).
- Comparison of the S_aO_2 value and the corresponding P_aO_2 with those expected when the HbO_2 curve is normal can identify deviations of the HbO_2 curve.

As for P_aO_2 above, anatomical shunts may create interpretation problems.

When compared to the **mixed venous SO_2 (S_vO_2),** a rough estimate of the relationship between O_2 supply and consumption may be made (see below).

	ACIDOSIS						ALKALOSIS				
	RESPIRATORY		METABOLIC			COMBINED	RESPIRATORY		METABOLIC		COMBINED
	Acute	Comp	Acute, AG ⇧[1]	Acute, AG ⇔[2]	Comp	Acute	Acute	Comp	Acute	Comp	Acute
pH	⇩	↓ or normal	⇩	⇩	↓	⇩	⇧	↑	⇧	↑	⇧
PCO_2*	⇧	⇧	⇩	⇩	↓	⇧	⇩	⇩	⇧	↑	⇩
HCO_3^-	↑	⇧	⇩	⇩	↓	⇧	⇩	↓	⇧	↑	⇧
BB	↔	⇧	⇩	⇩	↓	⇩	↔	↓	⇧	↑	⇧
BE	↔	⇧	⇩	⇩	↓	⇩	↔	↓	⇧	↑	⇧
Na^+-Cl^-	↔	↔	⇔	⇩	⇔	⇔	↔	↔	⇧	↔	↔
PO_2&	⇩	⇩	⇧*	⇧*	⇧*	⇩	⇧	⇧	⇩	⇩	⇧
sO_2	↓	↓	↓↑#	↓↑#	↓↑#	↓	↑	↑	↓	↓	↑

[1] Check for levels of lactate, ketones, urea, toxic agents.
[2] Check for loss of HCO_3^-, low Hb/albumin, excess Cl^-.
* Assuming normal ventilatory response.
& Deviation from expected level (relative to F_iO_2) if normal lungs.
# Higher P_aO_2 increase S_aO_2, severe acidosis can reduce it.

⇧ Increased. For BE: Positive value.
⇩ Decreased: For BE: Negative value.
↑ Increased, but less than initial change.
↓ Decreased, but less than initial change.
⇔ Variable, may be important for diagnosis.
↔ Variable, of minor importance.

Table 5-4. *Overview of expected changes in ABG parameters associated with various types of acid-base disturbances. Comp = state after renal compensation, AG = Anion gap.*

SOURCES OF ERROR AND CONFOUNDING FACTORS IN THE INTERPRETATION OF ARTERIAL BLOOD GASES.

HbO_2 saturation and the O_2 content of the blood: measured or calculated?

- The most important parameter for the O_2 transport capacity of the blood, the O_2 saturation of hemoglobin (SO_2), is often calculated from the pH, patient temperature, PCO_2, and PO_2 values by various algorithms (145, 146). Such calculations assume, however, that ***i)*** almost all of the hemoglobin in the blood sample are normally functioning HbA, that ***ii)*** the erythrocytes contain a close to normal level of 2,3-DPG and ***iii)*** there are no agents present that change the properties of the Hb molecule (see Part 2-3). If these assumptions are incorrect, substantial errors may arise, especially when the PO_2 is low.
- In most individuals, the bulk of Hb molecules is normally functioning HbA. With normal 2,3-DPG levels, the error introduced by calculating the corresponding SO_2 from the measured PO_2 is of little clinical importance when PO_2 > 10 kPa (75 mmHg). The calculations are, however, less accurate in severely ill patients, especially for the low PO_2 values often found in mixed- and central venous blood (see below). In patients where a significant percentage of the Hb molecules are functionally changed (e.g. COHb, MetHb, low intra-erythrocyte 2,3-DPG; see below) *or* the blood contains consists of Hb species other than the "standard" HbA (e.g. HbF, variant Hbs, Part 2-3), such calculations may yield very inaccurate results and lead to erroneous diagnostic conclusions.
- In many modern analyzers, SO_2 is measured directly by a *co-oximeter* incorporated into the instrument. It accurately measures not only the true *SO_2* (as O_2Hb) but also the presence of various Hb species (e.g. deoxygenated Hb (HHb), Hb changed by binding of CO (COHb), or changed by oxidation of the Hb Fe^{++} ions to Fe^{+++} ions (MetHb) *or* binding of sulfate to Hb molecules (SulfHb)). These are reported as a percentage (%) or as a fraction (F) of the total Hb (where the sum of fractions should be close to 1). The sum of percentages or fractions of analyzed species should be close to 100 or 1.00, respectively. It is important to be aware of

how local results are reported. While MetHb 0.4 % represents a low normal value, a MetHb fraction (FMetHb) of 0.40 indicates that 40% of the Hb is inactive as an O_2 carrier, which represents a life-threatening condition.

- Accurately measured O_2 saturation ($FHbO_2$ or "true" SO_2) is a prerequisite for reliable calculations of the relationship between O_2 delivery (DO_2) and – consumption ($\dot{V}O_2$) based on simultaneously drawn samples from arterial and mixed venous blood. It is therefore important for clinicians to be aware of whether the SO_2 value reported represents a directly measured or a calculated value.

Corrections of blood gas values for body temperature.

Most blood gas analyses are carried out with the samples at 37°C (98.6°F). Changes in body temperature also change the $[H^+]$ in body fluids including the blood; hypothermia decreases the dissociation of weak acids and reduces $[H^+]$ in aquatic media while the solubility of O_2 and CO_2 increases (Part 5-1). The opposite is true for hyperthermia. The values measured at 37°C (98.6°F) by the analyzers may therefore not accurately reflect the *in vivo* state in the blood of hypo- or hyperthermic patients. Most modern ABG analyzers can, however, recalculate the values to the actual state in the blood of patients with hyper- or hypothermia when the patient's temperature is entered.

For most patients, temperature corrections are of little importance if the deviation from normal is in the ±3°C range. For those with **marked hypothermia**, two alternative strategies for management of patients during controlled ventilation exist:

- The **alpha-stat** strategy consists of adjusting the ventilation to keep a *normal pH in the blood when measured at 37°C*, thus accepting hyperventilation and alkalosis at the patient's actual blood temperature.
- The **pH-stat** strategy consists of adjusting the CO_2 levels to keep *temperature-corrected pH close to 7.40 and the corrected PCO_2 around 5.3 kPa (40 mmHg)*.

An advantage of either of the two strategies for the patient outcome has not been definitively established (147, 148).

Interpreting P_aO_2 values in hypothermic patients.

In hypothermia, the arterial blood of a patient with normal lungs is in equilibrium with the alveolar gas, i.e. the P_aO_2 will be close to the PO_2 in the alveolar gas, which again is close to that calculated by the alveolar gas equation. The amount of O_2 dissolved in the fluid phase of the blood (intraerythrocyte fluid and plasma) is increased in hypothermia; about 30% more at a blood temperature of 20°C when compared to 37°C and about 16% more than at 27°C, compared to 37°C (149). This increase in P_aO_2 has, *per se*, little impact on the total C_aO_2 as only about 1.5% of the total O_2 in the blood is transported as dissolved gas under normal conditions (i.e. Hb 15 g/dl, Tp 37°C and pH 7.40, Part 2-3).

Hypothermia shifts the HbO_2 dissociation curve to the left (i.e. increased HbO_2 affinity); the S_aO_2 corresponding to any P_aO_2 is then higher than that at normothermia (fig. 5-18). As the normothermic S_aO_2 at a P_aO_2 of 13.3 kPa (100 mmHg) is already approximately 97.5% and cannot be higher than 100%, the increase in O_2 bound to Hb at a P_aO_2 in the normal range during hypothermia is modest. At lower values of P_aO_2, the impact of a leftward HbO_2 curve shift may be

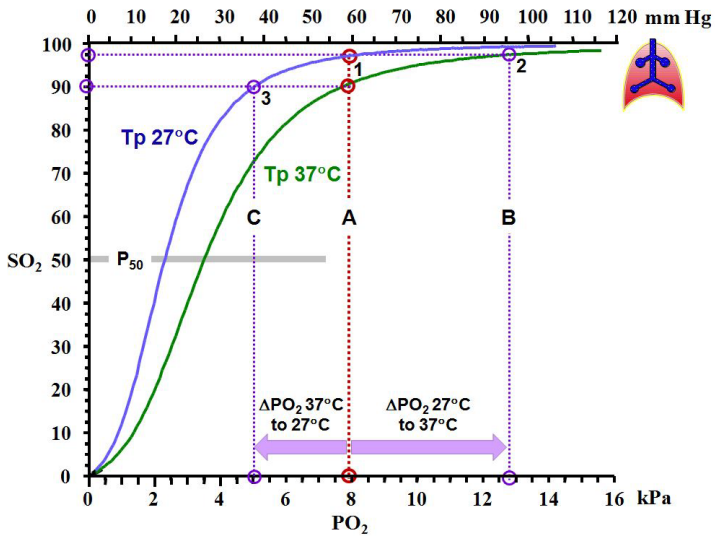


Figure 5-18. *Example of effect of differences in temperature on the HbO_2 curve. Lilac: Curve at 27°C, green: Curve at 37°C.* **1**: *Intersection with both curves for PO_2 8 kPa (60 mmHg).* **2**: *Intersection between normal HbO_2 curve at 37°C and SO_2 97%.* **3**: *Intersection between HbO_2 curve at 27°C and SO_2 91%. Vertical lines* **A**, **B** *and* **C** *indicate the corresponding PO_2 values; arrows indicate temperature-dependent differences in PO_2.*

substantial. With a P_aO_2 of 8 kPa (60 mmHg), a patient with normal temperature, pH and 2,3-DPG will have a S_aO_2 of approximately 91%, while the S_aO_2 of a hypothermic patient with a body temp of 27°C is approximately 97%. The arterial blood of the hypothermic patient thus contains 6-7% more O_2 per ml than that of a normothermic patient (fig. 5-18).

When a blood sample from a patient with a body temp of 27°C is warmed to 37°C in a blood gas analyzer, the HbO_2 curve shifts back to the right and assumes the normal position. The total amount of O_2 molecules in the sample is the same as at 27°C, but more of them are present as a dissolved gas. As the total amount of O_2 liberated from the Hb molecules is small, the change in S_aO_2 in blood with a normal Hb is minuscule, but the PO_2 increase may be substantial.

Calculation examples in hypothermia.

If a hypothermic patient's P_aO_2 is 8 kPa (60 mmHg) at 27°C, the S_aO_2 is approximately 97% (fig. 5-18); the amount of O_2 bound to Hb is approximately the same as that of normal blood at 37°C if Hb = 15 g/dl: (1.34 mlO_2/gHb x 15 gHb x 0.97) **= 19.5 mlO_2/dl**.
The amount of O_2 dissolved in the blood is 16% higher than at 37°C:
(0.0225 mlO_2/kPa x 8 kPa x 1.16) **= 0.21 mlO_2/dl**; both volumes are given as if measured at 37°C. The total O_2 content is thus less than 1% lower than that of normal blood at 37°C

Warming of the blood to 37°C results in a P_aO_2 of 12.8 kPa (96 mmHg), i.e. a difference of 4.8 kPa (36 mmHg), the amount of dissolved O_2 will be (0.0225 mlO_2/kPa x 12.8 kPa) **= 0.29 mlO_2/dl**, i.e. **0.08 mlO_2/dl** more than at 27°C. As each percentage point of S_aO_2 represents 19.5/100 **= 0.195 mlO_2/dl,** the amount of O_2 released from the Hb molecules as free gas is too small to change the S_aO_2, which will be essentially unchanged. At lower Hb values, like 6 g/dl, (1.34 mlO_2/gHb x 6 gHb x 0.97) **= 7.8 mlO_2/dl,** the amount of O_2 released from Hb will be about equal to the increase in dissociated O_2 per percentage point, and the S_aO_2 will decrease from 97% to 96%.

If the patient's P_aO_2 was normal, the difference between values at 27°C and 37°C would be even greater; the P_aO_2 reported after analysis at 37°C could be in the 18-20 kPa (135-150 mmHg) range and lead to the erroneous conclusion that the patient must have been receiving supplemental O_2 at the time of sampling. If, on the other hand, the reported P_aO_2 at 37°C was 8 kPa

(60 mmHg), the patient's real P_aO_2 at 27°C would be approximately 5 kPa (38 mmHg), which indicates a severe pulmonary dysfunction.

INTERPRETATION OF ANALYSIS OF BLOOD SAMPLES FROM NON-ARTERIAL SITES

Samples of blood for analysis of pH, PO_2 and PCO_2 may be obtained from many sites. In some patients, arterial samples may be difficult to obtain, in others, an arterial puncture may be considered too dramatic. In severely ill patients, analysis of blood gases from mixed or central venous blood can give important additional information about tissue oxygenation and perfusion (see above). A schematic drawing depicting various sampling sites is shown in fig. 5-19, the numbers in the figure corresponds to numbers in the text below.

Arterial samples: ①a: Mean value in pulmonary veins, ①b arterial samples. If there is no venous admixture due to extrapulmonary central right-to-left shunts, these values will be similar.

Mixed venous samples ② (usually from the pulmonary artery, samples from deep in the right ventricle are also reasonably representative). **The normal P_vO_2** value is approximately 5.3 kPa (40 mmHg); as this value is positioned on the steep part of the HbO_2 curve, small variations in P_vO_2 may cause substantial variations in the S_vO_2.
The normal S_vO_2 value is approximately 75% *or* 22-25% lower than arterial saturation (a (S_aO_2 – S_vO_2 difference of ≈ 22-25%). For the interpretation of these values to be useful as a reliable indicator of the balance between O_2 supply and consumption, the S_vO_2 must be *measured* by a co-oximeter or similar instruments *and* the S_vO_2/P_vCO_2 values must *always* be evaluated in relation to simultaneously measured arterial values, the Hb and body temperature.

- **If S_vO_2 is above normal**: C.O. (i.e. DO_2) may be higher than that corresponding to a normal or increased $\dot{V}O_2$ (i.e. high C.O.) *or* the $\dot{V}O_2$ may be decreased due to inhibition of the mitochondrial function (metabolic errors, toxins, drug effects, etc.).

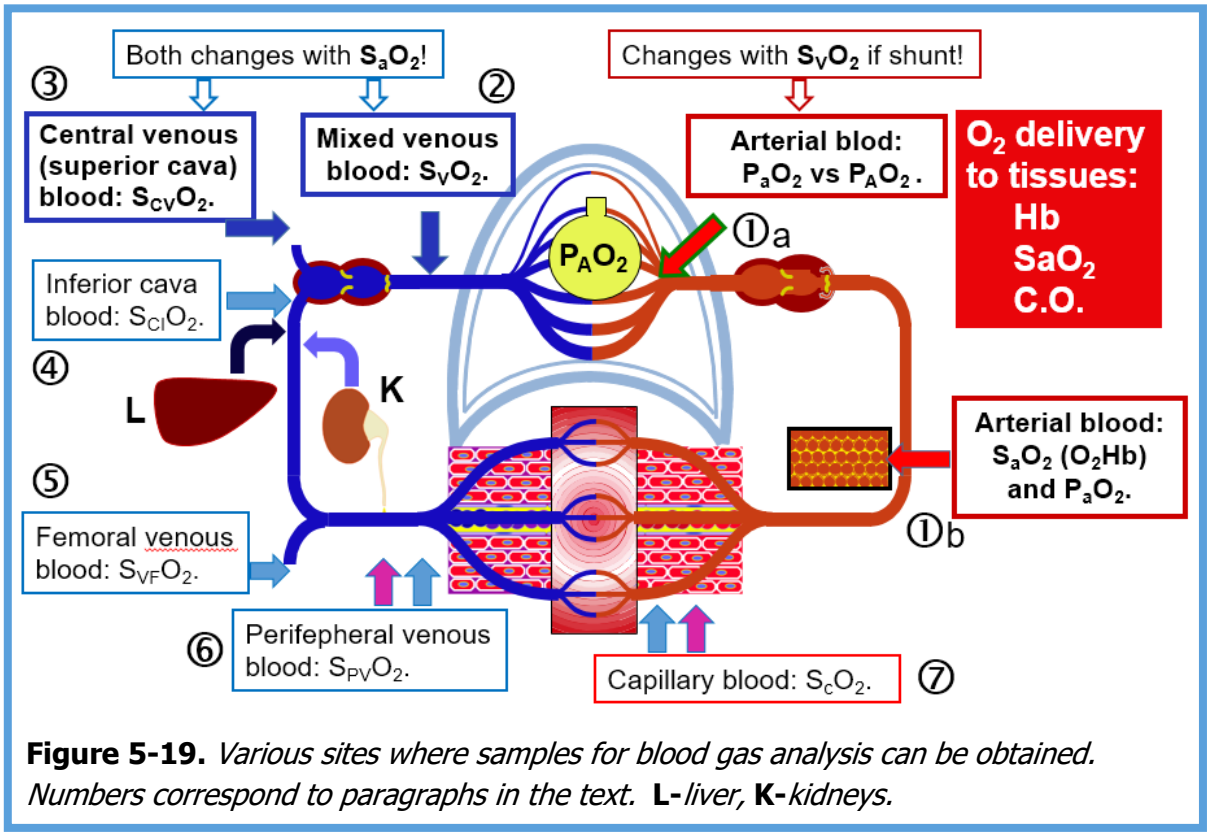


Figure 5-19. *Various sites where samples for blood gas analysis can be obtained. Numbers correspond to paragraphs in the text.* **L-***liver,* **K-***kidneys.*

- **If S_VO_2 is *below* normal**: Low DO_2 due to low S_aO_2, severe anemia, or low C.O.; increased $\dot{V}O_2$ without a compensating DO_2 increase may also result in a low S_VO_2.

When corrected for arterial O_2 content (S_aO_2 and Hb), calculations of C.O. are possible.

The P_VCO_2. Increased differences between P_VCO_2 and P_aCO_2 in patients may indicate circulatory failure; it can also represent a physiological change during heavy exercise.

Central venous samples ③ are obtained from a catheter with the distal orifice situated in the superior caval vein or another central, intrathoracic vein. Such samples are often used as a substitute for true mixed venous samples in calculations similar to those shown above.

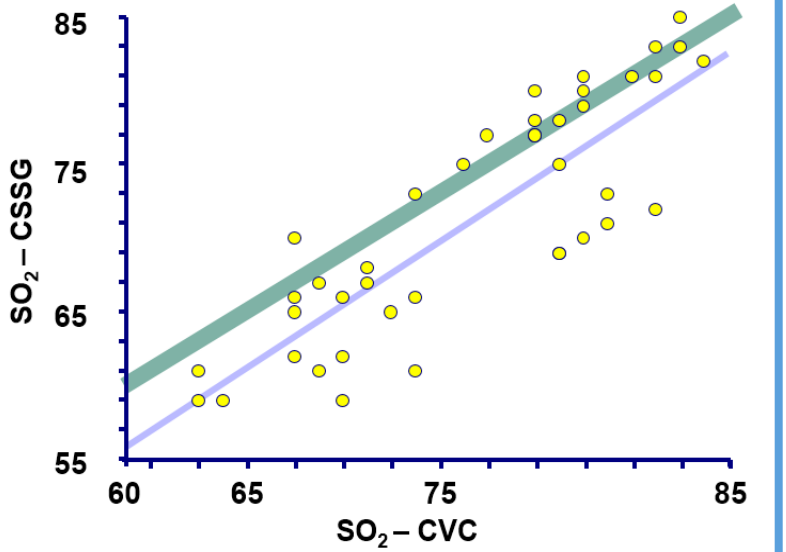


Figure 5-20. *SO_2 in samples of blood obtained simultaneously from the superior vena cava orifice of a PA catheter (y-axis) and from a separate central venous catheter (CVC- x- axis). Thin lilac line represents the line of best fit to the data, thick green line represents the line of identity. Unpublished data.*

The *mean* normal SO_2 difference between blood from a CVC and true mixed venous blood was, in one study, reported to be only 2-3%. In about 25% of the individuals examined, however, the difference was *higher than* 3% (150). In unselected patients, the mean difference may be in the 5-10% range, and the deviations in individual patients may be substantial (see also Part 3-4, fig. 3-32).

The SO_2 in samples obtained simultaneously from the cava superior orifice of a PA catheter and a separate CVC are not identical (fig. 5-20), indicating that the position of the sampling orifice may have a considerable impact on the result. This introduces an additional uncertainty as to whether a CVC sample should be considered representative of the true mixed S_VO_2.

Cava inferior samples ④ are usually obtained from a central catheter with a displaced distal orifice, or during sampling for scientific purposes. Due to the anatomic closeness of contributions from renal veins (with a high SO_2) and hepatic veins (with a low SO_2, see fig. 5-19) to each other and the right atrium, small variations in the position of the sampling catheter's orifice has a large impact on the results. In a clinical context, representative samples of mixed cava inferior blood are therefore difficult to obtain as well as interpret.

Femoral vein samples ⑤ are representative only of the conditions in the leg it is draining, and not of the whole organism. Such samples are to some extent used for scientific studies of exercise involving the legs (e.g. experiments where muscular exertion is performed on a bicycle). In a clinical context, they can be considered to represent a peripheral venous sample.

Peripheral venous sample ⑥ taken without venous stasis are reasonably representative of pH in the blood in resting, well-circulated persons. Mean values of PCO_2 are also close to the mixed venous values in persons with normal circulation, in hypoperfused patients, the individual

variation between arterial and peripheral venous values may be substantial (151, 152). During heavy exertion and/or hyperthermia in a warm environment, superficial skin veins function as arteriovenous shunts to dissipate heat; the blood flowing through such veins may then have close to arterial content of both O_2 and CO_2. On the other hand, during conditions of poor skin perfusion, the deviations from both arterial and mixed venous blood may be substantial.

Capillary blood samples ⑦ have traditionally been used to estimate the acid-base status in patients where arterial samples are hard to obtain or arterial puncture is deemed to represent an unnecessary intervention. Obtained correctly from well-perfused tissue (usually fingertips or heated earlobes in adults, scalp or heels in babies), they reflect arterial values, but with less accuracy than true arterial samples (153, 154).

In *perinatal medicine*, samples for blood gas analysis may also be obtained from the *umbilical cord vessels*. The interpretation of such samples will not be discussed here; readers interested in this topic are referred to reviews (155, 156).

TREATMENT OF ACUTE ACIDOSIS

Metabolic derangements often lead to acidosis.

Metabolic acidosis may, when severe, require rapid interventions directed specifically toward the underlying cause, which is seldom obvious based on the ABG values alone. To choose the correct interventions, additional laboratory tests, and clinical/pathophysiological insight are required for diagnosis and the correct choice of interventions.

In chronic states, various compensatory changes in buffer capacity may make the diagnosis of the underlying derangement difficult. The etiology of acute-on-chronic disturbances (e.g. lactate increase superimposed on chronic metabolic alkalosis) may be difficult to unravel and require an understanding of the basic principles of acid-base balance.

Several life-threatening diseases and conditions are, in addition to the deleterious effects of the diseases and conditions *per se*, accompanied by substantial acute changes in the acid-base balance of the organism. The association between acute lactacidosis and cardiac arrest, shock, and other serious diseases, combined with the negative effects of acidosis on C_aO_2 and circulation summarized above, led to the *previously common assumption* that

- Acidosis *per se* contributed to an unfavorable outcome, *and*
- Reversal of acidosis in the blood by infusions of a base would ameliorate the negative effects of acidosis and thus improve the outcome for the patients.

Correction of metabolic acidosis.

Consequently, reducing or abolishing metabolic acidosis by i.v. administration of buffers as soon as possible during cardiopulmonary resuscitation (157, 158) and circulatory shock (159, 160), as well as in other serious diseases, was strongly advocated from the 1920-ties to the 1960-ties. A solution of exogenous HCO_3^- ions (usually as $NaHCO_3$) was traditionally infused to replenish the HCO_3^- ions lost with increased excretion of CO_2 in severe metabolic acidosis (161). A commonly used formula for calculating the amount of base necessary to normalize the acid-base balance is based on the base deficit (or negative base excess: -BE)

Base (mmol) = -BE (mmol) x body weight (in kg) x 0.3.

Half of the calculated amount was usually infused initially, followed by a new ABG analysis and re-evaluation. If the –BE is 15 mmol/l in a person weighing 80 kg, the calculated amount of $NaHCO_2$ to be infused initially would be (15 x 80 x 0.3) x 0.5 = 180 mmol.

Another way to calculate the amount of $NaHCO_3$ for treating acidosis is based on HCO_3^-:

Base (as mmol $NaHCO_3$) = (desired – patient HCO_3^-) x bodyweight (in kg) x 0.4.

If patient HCO_3^- is about 14 mmol/l, weight as above, and full correction is desired, the amount needed would be ((24-14) x 80 x 0.4) = 320 mmol or, using the principle of correcting half of the derangement, 160 mmol.

In acute metabolic acidosis, a dramatic increase in the depth of ventilation with a reduction of CO_2 in arterial blood by approximately 50% or more, is common. In severe acidosis of several hours duration, P_aCO_2 may be reduced to values in the range of 22-30% of normal (162, 163), and the HCO_3^- levels become even lower due to the increased $[H^+]$ (see Part 5-1).

The ability to reverse acidosis with $NaHCO_3$ depends on the ability to *excrete* the generated increase in CO_2 (see above); if this fails, the metabolic acidosis will be accompanied by a CO_2 increase and result in a clinical picture of a mixed metabolic- and respiratory acidosis. Consequently, other solutions of base (Tribonate®, Tromethamine (also known as THAM or TRIS), etc.), less dependent on pulmonary function, have also been used for the correction of acidosis.

Respiratory derangements and acidosis correction.

If an acute acidosis is respiratory, increased chemoreceptor stimulation by H^+ and CO_2 produces little further change in ventilation. Antidotes against a toxic concentration of drugs or agents that reduce the efficiency of the respiratory muscles, *or* manual or mechanical support of ventilation, are treatments of the underlying problems. In extreme situations, especially with severe combined respiratory and metabolic acidosis, tromethamine (THAM), which does not depend on ventilation for its buffering efficiency, can be utilized. This agent depends on renal excretion for elimination, the amount that can be infused in renal failure patients is therefore limited. Concentrated solutions of THAM must be given through a central line, but dilute solutions can be given peripherally. An overview of the use of THAM in various situations is given in ref (164).

The benefits of buffering in acute acidosis are still debated.

Whether acid-base changes truly represent a significant additional risk factor *per se* or should be considered only as an additional consequence of one or several ongoing pathophysiological processes, is uncertain. In severe lactacidosis resulting from maximal exertion (96), the surplus H^+ ions are generated by the working muscles; cells in all other tissues are exposed to extracellular acidosis. No negative effects, except for fatigue, are seen even if the pH may decrease to ≈ 6.80 (96). The effect in acute animal experiments, where acidosis is induced by infusions of acid (165, 166), is difficult to interpret, as the degree of *intracellular* acidosis in various tissues as a result of the extracellular one is uncertain. In one study, an infusion of lactic acid that decreased pH by 0.2 pH units resulted in only a small and non-significant decrease in intracardiomyocyte pH (167). Whether this holds true also for more severe acidosis is unknown.

Even if acidosis in the arterial blood can be ameliorated or abolished by buffer infusions in most types of metabolic acidosis, the beneficial effect of such attempts to normalize an acute acid-base balance is still debated (168). Acidosis treatment with base infusion was routine during resuscitation after cardiac arrest half a century ago (169), but the effect on the outcome for the patients is highly controversial. Buffer infusion during short-term resuscitation (< 10 minutes) is therefore no longer recommended (170, 171) as a routine. Such buffer treatment may, under certain conditions, even have negative effects on the intracellular pH (28, 172). In most situations, acidosis is a symptom of an underlying disease or condition; treating the etiology (when

possible) is more important than treating the symptom by buffering the acidosis. Consequently, some authors argue against any use of buffers in acidosis, regardless of the severity of the acidosis (173, 174).

Even if definitive proof of a beneficial effect of buffering of acidosis is lacking (175, 176, 177), many physicians will treat a metabolic acidosis with buffer solutions when pH < 7.10-7.15, especially in patients whose circulation is unstable and the condition leading to acidosis cannot be expected to resolve within minutes to few hours. The adverse effects of severe acidosis on the C_aO_2 in patients with respiratory failure and a sub-normal P_aO_2, as described in ref. 48, constitute a logical argument for acidosis correction in such patients. In addition, the negative effect of severe acidosis on myocardial function (128) may inhibit the desired increase in C.O. during hypoxemia. Scientific proof for increased survival with such treatment has not been presented; due to the heterogeneous etiology of acute metabolic acidosis and the difficulties involved in this type of clinical research, definite proof of a beneficial effect will be difficult to establish.

Most of the investigations that failed to show a positive effect of buffer treatment of acute acidosis deal, however, with acidosis arising under conditions of low- or no tissue flow, where the hypoxic insult to the organism may be so massive that effects of interventions other than re-establishing tissue flow and oxygenation are difficult to detect. A possible treatment effect in other, less dramatic, conditions has not been definitively proven nor disproven; in some types of intoxications, however, buffering seems to have a positive effect (178, 179). Alkalization of the urine in massive rhabdomyolysis represents a separate indication for buffer infusions (180), and reducing the $[H^+]$ in severe acidosis in patients with a concomitant respiratory failure and low P_aO_2 may increase the O_2 content of the blood (see above and Part 2-3). In patients with chronic renal diseases, adding bicarbonate to the diet or by infusion may be beneficial (139).

TREATMENT OF ACUTE ALKALOSIS

Emergency treatment of alkalosis corresponding to pH at or below 7.55 is normally not necessary, provided the patient is asymptomatic. Correction of metabolic alkalosis that requires treatment normally takes hours to days and involves the intravenous administration of potassium and other chloride compounds (KCl, NaCl, arginine hydrochloride, refs 81, 182), if necessary supplemented by drugs that promote K^+ and H^+ retention in urine (e.g. acetazolamide, aldosterone antagonists). Diluted hydrochloric acid (HCl) have also be given through central venous catheters in extreme situations (183, 184). Acute respiratory alkalosis in otherwise healthy, spontaneously ventilating persons is treated by increasing the ventilatory dead space (breathing through a paper bag or kitchen roll). The use of increased dead space in patients on CPAP or patient-controlled assisted ventilation (see Part 4-4) is usually not advisable, as the result often will be an increased workload for the respiratory muscles.

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APPENDIX: UNITS AND NUMBERS, WEIGHTS AND MASS, PRESSURES, DIFFUSION AND SOLUBILITY, SOME PHYSICS

INTRODUCTION

In clinical as well as scientific medicine, measurements of quantities, flow and pressures are important not only for understanding physiological and biochemical mechanisms and establishing diagnoses, but also for evaluating the effect of various treatments on diseases. The need for accuracy varies with the *purpose* for obtaining measured or calculated parameters. At the bed-side, a clinician will usually draw the conclusion of circulatory failure regardless of whether the cardiac output of a normothermic adult with normal body mass is measured as 3.4, 3.6 or 3.8 l/min. On the other hand, to assess whether or not the chosen treatment regime improves the circulatory state, the precision of measurements *before* and *after* the intervention is crucial for reaching the correct conclusion about the treatment effect.

During the early stages of modern medicine and science in general, weights, volumes, and dimensions were measured in units commonly used for official and commercial purposes in each country. Scales and weights were easy to procure; units of weight were therefore convenient to use as an expression of mass. The height of a column of fluid (water, blood, etc.), defined the magnitude of pressure. As the gas pressure of one atmosphere is equal to a water column of 10.13 meters, the systolic blood pressure of a hypertensive patient may be equal to a 2 to 2.5-meter column of water, aquatic fluids are impractical for the measurement of higher pressures. Columns of mercury were therefore used for such measurements (fig A-1). Unfortunately, despite decades of attempts at standardization, there is still some variation in the *units* used for such measurements between, as well as within, countries and regions.

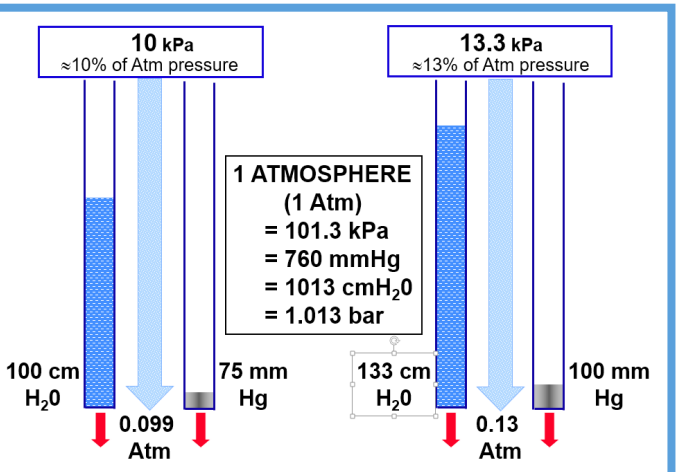

Figure A-1. *Relationship between pressures measured as cmH_2O, atmospheres* (Atm)*, mmHg, and kPa. At 1 Atm, the partial pressure of a gas as measured in kPa is close (but not identical) to the percentage.*

The origins of today's metric system can be traced back to around 1670 in France, a metric system was adopted by the French government at the end of the seventeenth century. Its use spread rapidly to most of the other European countries; consequently, in the laboratories of French and German researchers, the metric system (using units like grams, liters, cubic decimeters, and meters) was common (1). In England, as well as in the USA and other former colonies, many scientists recognized the merits of the metric system; it was not, however, adopted by the government for common use. Units like pounds, pints, gallons, feet, and inches, therefore, continued in England; these units were standardized at the beginning of the 18th century as "Imperial Units" (2). Such units are no longer used in modern scientific medical literature; related units are, however, still commonly used in the USA for commercial and other purposes.

The SI system, conversion factors from conventional units.

Blood chemistry: Common laboratory values, SI and conventional.

Electrolytes	SI (and SI accepted) units	Conversions		Older (Conventional) Units
Na^+	136-142 mmol/l	x 1	x 1	136-142 mEq/l
K^+	3.5-5.0 mmol/l	x 1	x 1	3.5-5.0 mEq/l
Ca^{++} total	2.15-2.50 mmol/l	x 0.5	x 2	4.3-5.0 mEq/l
Ca^{++} ionized	1.15-1.35 mmol/l	x 0.5	x 2	2.3-2.7 mEq/l
Mg^{++}	0.70-0.95 mmol/l	x 0.5	x 2	1.4-1.9 mEq/l
P (as phosphates)	1.12-1.45 mmol/l	x 0.5	x 2	2.25-2.9 mEq/l
Cl^-	97-107 mmol/l	x 1	x 1	97-107 mEq/l
SO_4^{--}	0.09-0.63 mmol/l	x 0.5	x 2	0.18-1.26 mEq/l
Others				
Hemoglobin*	7.45-9.93 mmol/l	x 0.6206	x 1.6113	12-16 g/dl
Albumin	34-48 g/l	x 10	x 0.10	3.4-4.8 g/dl
Glucose	4-6 mmol/l	x 0.05551	x 18.0148	70-110 mg/dl
Urea	2.6-8 mmol/l	x 0.0357	x 28.0112	8-23 mg/dl
Creatinine	45-105 µmol/l	x 88.4	x 0.0113	0.6-1.2 mg/dl
Lactate	0.3-1.5 mmol/l	x 0.111	x 8.8495	3-11.3 mg/dl
Bilirubin	3-25 µmol/l	x 17.1	x 0.0585	0.3-1.2 mg/dl

Table A-1. *Common laboratory values in conventional and SI units. *The SI Units for Haemoglobin shown here is for the Hb monomer and not for the whole Hb molecule (see text below).*

The units used to define *mass, concentrations of substances*, *volumes,* and *pressures*, as well as analytical methods and equipment, are now relatively standardized in the western world. A few exceptions still remain in the USA (see below). The predominant measurement system in the natural sciences, including medicine, the **International System of Units** (abbreviated **SI system** after the French "*Le Système International d'Unités*") is based on the metric system. In Europe and most of the world, the concentrations of substances in body fluids are given as SI units like **moles** per liter (**mol/l**), see below, or, usually, fractions of moles like *millimoles* (*mmol,* 10^{-3} mol), *micromoles* (*µmol,* 10^{-6} mol) or *nanomoles* (*nmol,* 10^{-9} mol). In older scientific literature, however, results were reported using the units in common use at that time ("*conventional units*").

The introduction of SI units in clinical medicine in the USA has hitherto met with limited success, although they are common in the scientific literature. Much of the international medical scientific literature originates from Europe or the USA; it is, therefore, important to be aware of the difference in units used to denote identical quantities and some of the most important conversion factors. Even in countries that have adopted the SI system in principle, the use of some traditional units (e.g. mmHg for hydrostatic pressures, cmH_2O for airway pressures, grams per dl or l for Hemoglobin and Albumin, temperatures given in °C instead of °K (Kelvin)) are so well entrenched in the clinical community that a radical change is unlikely to occur in the near future. In the USA, the quantity of many substances (e.g. glucose and urea in the blood) is still often given in units of weight, like mg/dl or liter. Comprehensive

Temperature measurement and units.

°C	°F	°K	°C	°F	°K
-50	-58.0	223	30	86	303
-40	-40.0	233	32	89.6	305
-30	-22.0	243	35	95	308
-20	-4.0	253	37	98.6	310
-15	5.0	258	38	100.4	311
-10	14.0	263	39	102.2	312
-5	23.0	268	40	104	313
0	32.0	273	41	105.8	314
5	41.0	278	42	107.6	315
10	50.0	283	43	109.4	316
15	59.0	288	50	122	323
20	68.0	293	75	167	348
25	77.0	298	100	212	373

Conversion equations.

$$t°C = \frac{(t°F - 32)}{1.8} \qquad t°F = (t°C \times 1.8) + 32 \qquad t°K = t°C + 273$$

Table A-2: **Temperature conversions.**
For temperatures measured as degrees Celsius (°C), Fahrenheit (°F) and Kelvin (°K).

tables for conversion from conventional to SI units within medicine (3) and other fields (4, 5) have been published; many internet sites also offer conversion tables and calculators. Normal values and conversion factors for some substances commonly measured in clinical medicine are shown in Table A-1. In addition, the use of Fahrenheit (°F) as the unit for measurement of temperature remains common in the USA (see Table A-2 for conversions).

UNITS OF MEASUREMENT.

QUANTITIES commonly measured within the field of medicine are

- **The concentration of various molecules, electrolytes,** and **ions** in the blood and other body fluids. Such concentrations may be given as *units of weight*, as *units defining the number of molecules* (moles, see below), or as *arbitrary units* derived from various assays.
- **Volumes of fluid within the cardiovascular system** (e.g. blood volume, volumes within the cardiac chambers) and the interstitial space (interstitial fluid), as well as the *flow of volumes* per unit of time (volume/time), e.g. of blood pumped by the heart (liter/min).
- **Volumes of gas within the airways** and the volumes inhaled/exhaled with each breath (tidal volumes). Also, the volumes of gas (e.g. oxygen, carbon dioxide) transported by the blood and consumed or generated by the metabolic processes. In the latter, volumes can be substituted by an unit expressing the number of molecules, the *mole* (see below).

Volumes are usually given as liters (l) or fractions of a liter (deciliter, milliliter, microliters, etc.). The volume of a substance as a solid or a fluid changes with temperature, the change in volume of aquatic fluids from room to body temperature is small (about 0.5% increase) and is of little consequence in the medical profession. The volume of gases like O_2 and CO_2 changes about ten times more within this temperature range; gas volumes measured at different temperatures must therefore be corrected for the temperature effect (see below) before comparisons.

PRESSURES commonly measured in medicine are

- **Hydrostatic pressures**, i.e. pressures exerted by body fluids, of which arterial, capillary, venous and intracardiac pressures are the most commonly measured. They are usually given as *millimeters of mercury* (**mmHg**) or *cm of H_2O* (**cmH_2O**)*, relative to ambient pressure*.
- **Osmotic/oncotic pressures,** i.e. pressures exerted by molecules dissolved into fluids. These pressures are important for regulation of the fluid balance across cell membranes and capillary walls. The concentration of such molecules are usually given as *milliosmoles/l* (**mOsm/l**); the pressure exerted by the osmotic effect in **mmHg**.
- **Gas pressures** (also called gas tension) of interest in medicine can be divided into
  - The physical pressure exerted by ambient gases on the body by the environment (during diving and at high altitudes), and of gases within body cavities (often lungs), *and*
  - The pressure exerted by gases dissolved in body fluids (e.g. blood, plasma, and interstitial- and intracellular fluid).

Gas pressures are usually given as *absolute pressure* using units such as *kilopascal* (**kPa**), **mmHg** or **Torr**, **Bar,** or *Atmospheres (***Atm**) (see fig. A-1 and Table A-5). At identical pressures, however, the *number of gas molecules* in a gas and as gas dissolved in a fluid is different (see below). The level of difference depends on the *solubility* of the gas in the fluid (here, the aquatic fluids in the body).

Symbols and abbreviations (see also Part 5-4).

Abbreviations and symbols are not universally standardized. Both *p* and P are in common use as a designation of gas pressures, l and L both indicate liter, etc. **Decimal separation** symbols also vary between different countries. Almost all European countries use the comma, as in 37,6°C

for normal body temperature; the USA and most Asian countries use a point (or dot), as in 37.6°C. The latter is used as the decimal separator in this compendium.

Gas pressure. The use of symbols for gas pressures varies somewhat; recommendations for their use differ between various countries (6, 7, 8). In physiological expressions and equations, the letter **P** usually denotes the actual pressure measured, while Δ**P** (Delta P) denotes the magnitude of a *change* in pressure (the Δ symbol is also used to denote the change in many other parameters). In some countries, lower-case letters are used in these symbols (e.g. lower-case **p**). The pressure of a **gas** (e.g. O_2) **in the alveoli** is indicated by the symbol upper case **A** (**P_AO_2**), the pressure of the gas in **arterial blood** by lower-case **a** (**P_aO_2**); in **capillaries** by lower-case **c** (**P_cO_2**), in **mixed venous blood** usually by **v** (**P_vO_2**) and in **central venous blood** by **C** (**P_CO_2**) **or** (**$P_{Cv}O_2$**). The symbol for barometric pressure in ambient gas is **P_B**, and that for water vapor pressure is **P_{H_2O}**.

The **oxygen saturation** of hemoglobin is normally indicated by the symbol **S** (for *saturation*). It is usually given as a percentage of the theoretical maximal (100%) saturation, but may also be presented as the saturation *fraction* ($FHbO_2$) of the maximum (SO_2 100% = $FHbO_2$ 1.0, SO_2 60% = $FHbO_2$ 0.6). Both oxygen saturation and pH in arterial and venous blood are indicated in the same way as for PO_2 (**S_aO_2**, **S_vO_2**, **pH_a**, **pH_v**). Oxygen saturation measured utilizing *pulse oximetry* is usually denoted **S_pO_2**.

The symbol for **volumes** (e.g. ventilation volumes) is **V**, that for **blood flow** is **Q** or **$\dot{Q}$**; the former is used in this compendium. The blood flow to the whole organism is normally identical to the cardiac output; the common abbreviation in clinical medicine is **CO.** This is unfortunately also the common abbreviation for the gas carbon monoxide; to avoid confusion, the abbreviation **C.O.** is used to indicate the cardiac output in this compendium. **Content** (e.g. content of O_2 in the blood) is usually indicated by the symbol ***C* or C**. The oxygen content of arterial and venous blood is written as **C_aO_2** and **C_vO_2**, respectively. The symbol for oxygen consumption is **$\dot{V}O_2$**.

Units employed for measurements of **pressure** vary according to both the type of pressure involved and the field or profession within which it is measured (see below). Basic physiological research, upon which much of today's knowledge is built, was carried out before the invention of modern electronic measuring equipment. Pressures were easiest, and most accurately, measured utilizing the height of columns of mercury or water, the use of such units has endured within some fields. As calibration was carried out by switching a U-shaped piece of tubing or a stopcock open to the pressure of the surrounding air, hydrostatic pressures are traditionally given as the pressure *above* or *below* the ambient atmospheric pressure.

Magnitudes and notations.

Dealing with very small and very large numbers is cumbersome and may easily lead to calculation errors. The use of **logarithms** is a kind of shorthand for displaying very large or very small numbers; in medicine, logarithms usually refer to powers with 10 as a base ($\log_{10}$). The exponent or power corresponding to a number indicates how many times 10 must be multiplied by itself to give that number. Numbers between 1 and 0 have negative exponents, numbers between 1 and 10 have exponents between 0 and 1, and those above 10 have exponents larger than 1. The normal concentration of H^+ ions in arterial blood, which is 0.000 000 040 mol/l, is written as $10^{-7.40}$ mol/l; the number of bytes in a memory stick with 128 gigabytes is 128 000 000 000 bytes may be written as $10^{11.10720997}$ bytes (see also table A-3).

Prefixes and symbols in the metric system (log_{10})

Towards infinity.

Exponents	Means	Prefix	Symbol
10^{12}		tera	T
10^{9}	1 000 000 000	giga	G
10^{6}	1 000 000	mega	M
10^{3}	1 000	kilo	k
10^{2}	100	hecto	h
10^{1}	10	deca	da
10^{0}	1	—	—
10^{-1}	1/10	deci	d
10^{-2}	1/100	centi	c
10^{-3}	1/1 000	milli	m
10^{-6}	1/1 000 000	micro	µ
10^{-9}	1/1 000 000 000	nano	n
10^{-12}		pico	p
10^{-15}		femto	f
10^{-18}		atto	a

Towards zero.

Table A-3: *Examples of exponents and prefixes.*

In **scientific notation**, very small and very large numbers are expressed as a number between 0 and 10, multiplied with 10 raised to an exponent that defines the magnitude of the number. In the examples above, the concentration of free H^+ would be written as 4×10^{-8} and the number of bytes as 1.28×10^{11}.

A related practice is called **engineering notation**; here, the number is given as 1-3 digits before a decimal point, multiplied by 10 raised to an exponent in steps of three (i.e. units of a thousand); e.g. 10^3, 10^6, 10^9, etc. and 10^{-3}, 10^{-6}, 10^{-9}. The examples above, given in engineering notation, would be 40×10^{-9} and 128×10^9. In medicine, the units for measurements are usually given in magnitudes corresponding to engineering notation, i.e. in steps of 10^3 or 10^{-3}. One kiloPascal is 1000 (10^3) Pascals, one millimol is 1/1 000 (10^{-3}) mol and one micromol is 1/1 000 000 (10^{-6}) mol. A nanomol is 10^{-9} mol. Some of the commonly encountered magnitudes and prefixes are shown in table A-3.

THE NUMBER OF MOLECULES IN SOLIDS, FLUIDS, AND GASES: THE MOLE

In chemical reactions, the interaction between molecules and ions follows certain rules, which define the number of various entities involved in the reaction. Two substances with equal weights usually contain a different number of molecules. The volume of a gas containing a given number of molecules changes as a result of variations in both pressure- and temperature (see *gas laws* below); the number of molecules in a solution and a gas is, however, important for its properties (e.g. osmotic pressure, gas pressure, ability to sustain biochemical reactions). Ideally, all measurements of concentrations should contain information about the number of molecules per volume; in scientific medicine, it makes sense to focus on the number of molecules in a gas or a fluid instead of the gas volume or units of weight.

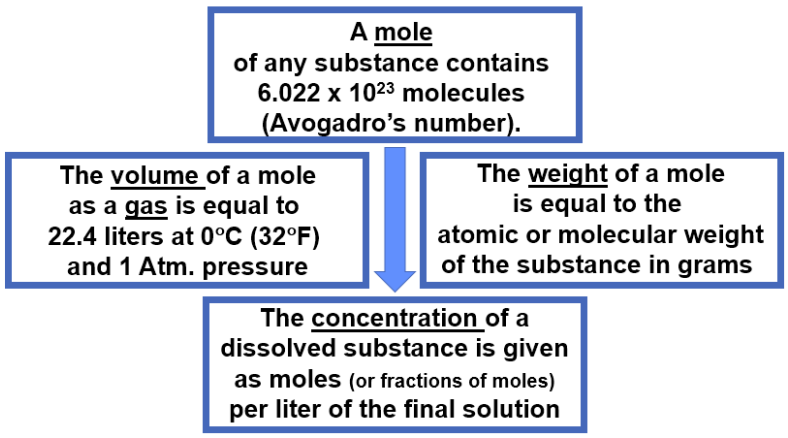

Figure A-2. The mole: *Volume as gas, weight and as a measure of concentration.*

The unit **mole** (mol) in the SI system represents a bridge between the number of molecules, weights, and volumes. **A mole of any type of substance** (e.g. *atoms, ions, or molecules*), whether present

as a **gas, a fluid,** or in **solid form,** contains the **same number of molecules** (**Avogadro's number**, approx. 6.022 x 10^{23} molecules, fig A-2) (9). The **weight** of a mole of any substance is equal to the **atomic weight** (for atoms and ions) or the **sum of atomic weights** (for molecules consisting of more than one atom). **Dalton** is another unit used to define the atomic weight (or molecular weight); as carbon (C) has an atomic weight of 12, one Dalton is defined as 1/12 of the atomic weight of a carbon nucleus. The molecular weight of larger molecules is often given in Daltons, and the mass of large molecules (e.g. many proteins) is often given in units of 1000 (kilo) Da, as kDa.

Atomic (At_W) and/or molecular# (Mol_W) weights.

	At_W		At_W	Mol_W		Mol_W
	g/mol		*g/mol*	*g/mol*		*g/mol*
Na	22.99	**O / O_2**	16	32	**Hemoglobin**	64 500
Cl	35.457	**H / H_2**	1.008	2.016	**Albumin**	66 500
K	39.1	**N / N_2**	14.008	28	**Glucose**	180
Ca	40.08	**CO_2**		44	**Urea**	60
Mg	24.32	**H_2O**		18	**Creatinine**	113
C	12.011	**Air**		29	**Bilirubin**	585

Approximate values.

Table A-4: *Atomic and molecular weights of some substances of interest in clinical medicine.*

In medicine, the weight of a mole is usually given in grams; if a substance has a molecular weight of approximately 180 g (e.g. the sum of the atomic weights of atoms that constitute the glucose molecule), 180 g of the substance dissolved in water to a total volume of one liter gives a concentration of 1 mol/l. The concentration of major electrolytes, as well as O_2 and CO_2 in the blood and other body fluids, exists in concentrations substantially lower than a mole (table A-4). In clinical medicine, the notation *millimoles/liter (mmol/l), i.e.* one-thousandth of a mole/l, is therefore the most common unit used for concentrations.

Conversion of hemoglobin concentrations from g/dl to mmol/l may create some confusion (see also Part 2-3 – Hemoglobin). The hemoglobin molecule consists of four globulins of almost equal weight (the *monomer* s – weighing about 16 125 Da each); as each globulin binds one O_2 molecule, the molecular weight of one of the globulins is often used as a conversion factor. The logic of this tradition is that by giving the Hb value in mmol/l calculated for the monomer, the same value multiplied by the HbO_2 saturation fraction indicates the mass of Hb-bound O_2 in mmol/l. The molecular weight of the whole Hb molecule (the *tetramer*) is, however, about 64 500 Da, the conversion factor from g/dl to mmol/l is then 0.1551 mmol/l when using the tetramer as a base for molar concentration, see also Table A-1).

Ions are atoms or molecules with net positive or negative charges. The unit milliequivalents per liter (mEq/l) was previously used to quantify concentrations of ions in the blood; this practice has largely been substituted by using mmol/l also for ions. To illustrate points connected with the electroneutrality of fluids, however, mEq/l is still sometimes used (e.g. for depicting the balance of ions in body fluids as presented by a Gamble diagram, Part 5-2). For ions with a single charge (e.g. Na^+), concentrations given in mEq/l and mmol/l are the same; for ions with more than one charge (e.g. Ca^{++}); the value in mEq is the mmol/l value multiplied by the number of charges (Table A-1).

The **volume** occupied by a **mole of an ideal, dry gas** when measured **at 0°C** (32°F) and a pressure of **one atmosphere** (**STP** – *Standard Temperature and Pressure* - see gas pressures below) **is 22.4 liters**. Gases like O_2, CO_2, and water vapor are not ideal gases, but their behavior within the temperature and pressure ranges relevant to clinical medicine is close enough to justify using the ideal gas laws (see below). This means that

- **One liter** of **any gas under STP conditions** contains (1 mole/22.4 l) = 0.0446 mol/l/atm *or* **44.6 mmol/l/atm.** As 1 Atm is equal to 101.3 kPa *or* 760 mmHg, a liter contains (44.6 mmol/l/101.3 kPa) = **0.44 mmol/l/kPa** *or* (44.6 mmol/l/760 mmHg) = **0.059 mmol/l/mmHg**.
- **In a mixture of gases**, the fraction of each gas *is proportional to its partial pressure.* The **molecular content** of a **gas** with a pressure of **5.3 kPa** (40 mmHg) at sea level is calculated as ((44.6 mmol/l/101.3 kPa) x 5.3 kPa*) or* ((44.6 mmol/l/760 mmHg) x 40 mmHg) = **2.35 mmol/l.**
- As dry air contains 20.9% O_2 (a fraction of 0.209), **one liter of air under STP conditions** contains 44.6 mmol/l/Atm x 0.209 = **9.32 mmolO_2/Atm**. If the consumption of O_2 by an organism at rest is 250 ml/min and the production of CO_2 is 200 ml/min (both at STP), the **mass of O_2 consumed** per minute is (0.250 l x 44.6 mmolO_2/l) = **11.2 mmolO_2/min** and that of **CO_2** generated (0.200 l x 44.6 mmolCO_2/l) = **8.9 mmolCO_2/min**.

Moles per volume and the effects of temperature.

Solids and liquids. The volume occupied by a mole of a solid substance or a liquid changes only modestly within the temperature range from 0°C to 40°C (32°F to 104°F); the errors introduced by omitting corrections for temperature are of little importance in clinical medicine.

Gases. The change in volume of a mole of gas when temperature changes are, however, of greater importance. The volume of expiratory gas, containing the same number of moles, will be different depending on whether the volume is measured by a flow meter close to the mouth (where gas temperature is close to body temperature), by a flow meter 1-2 m distant from the mouth (between body and room temperature as in most ventilators) or by a tank spirometer (room temperature). Conversions from volumes of gas to mmol/l *or* units of weight assume that measured gas volumes are converted into volumes of dry gas at 0°C (32°F) and at 1 Atm (Standard Temperature and Pressure Dry gas – STPD); for all calculations involving O_2 consumption and CO_2 production, gas volumes must always be recalculated to STPD conditions. At -40°C (-40°F), a very cold winter's day indeed, the volume of a gas containing a given number of molecules will be almost 30% smaller than that at room temperature.

According to the Universal gas law (below), the volume of a gas increases by about 5% from room air to body temperature (22°C to 37°C *or* 71.6°F to 98.6°F) and by about 13.5% from STPD to body temperature (0°C to 37°C *or* 32°F to 98.6°F), while the number of gas molecules stays constant. At **body temperature**, a **mole of gas**, therefore, occupies (22.4 l x 1.1355) = **25.4 liters**; failure to correct for the increased volume at 37°C will thus introduce an error of 13.55% when calculating the number of molecules in a sample of gas.

- 1 liter of **gas at body temperature** (37°C, 98.6°F) at sea level contains fewer molecules than at STP: (1/25.4) = *0.03937 mol* or **39.37 mmol/l/atm** vs 44.6 mmol/l/atm STPD.
- The content *per kPa* in a mixture of gases (see above) is about 100 times smaller: (39.37/101.3) = **0.3886 mmol/l/kPa,** in *mmHg*: (39.37/760) = **0.0518 mmol/l/mmHg**.

PRESSURES: TYPES, UNITS, ABSOLUTE AND RELATIVE.

Units used to quantify pressures vary *between* different countries and also between different fields of the natural sciences *within* the same country. The most common units for measurements of various types of pressure in clinical medicine are presented below.

- **Hydrostatic (fluid) pressures** are usually measured in **mmHg,** or sometimes **cmH_2O.**
- **Osmotic pressures** are usually measured as **mmHg** (or sometimes in **kPa**).
- **The concentration of Osmoles** (see below) is usually measured in **mOsm/l.**

- **Colloid osmotic (oncotic) pressures** are usually measured in **mmHg.**
- **Gas pressures** may be measured in **kPa, mmHg** *or* **Torr, cmH_2O, atmospheres,** or **fraction of an atmosphere.** The pressure of a **gas dissolved in a fluid is usually** measured in **kPa** (Europe and most of the world) or **mmHg** *or* **Torr** (USA).

See fig A-1 and Table A-5 (at the end of this part) for comparison of the various units.

Pressures may be measured as

- **Absolute** (e.g. most gas pressures, atmospheric pressures).
- **Relative to atmospheric pressure** (e.g. hydrostatic pressures in body fluids, airway pressures).
- **Relative to the surrounding pressure** (transmural pressures - pressures inside an organ corrected for the pressure (of tissue/fluid/gas) outside the organ – see below and fig. A-7.).

Hydrostatic pressure.

Originally, the pressure so named represented the weight of a column of water, but the term is commonly used for measuring the pressure of any fluid. In medicine, pressures exerted by the blood on the vessel- and cardiac walls and their surroundings are examples of hydrostatic pressures. Measurement of fluid pressures within arteries, "blood pressure" or ABP, is the most common hydrostatic pressure measured in medicine; also pressures within intrathoracic veins (central venous pressure, CVP), the pulmonary artery (PA pressure), and the chambers of the heart are useful for advanced monitoring of the circulation and diagnosis (see Part 3-4). Hydrostatic pressures measured directly through cannulas inserted into arteries, veins, or cardiac chambers are denoted *invasive pressures*. Today, they are usually measured utilizing pressure transducers coupled to electronic measuring devices.

Despite the introduction of the SI system units in clinical medicine, hydrostatic pressures are still measured in traditional, non-SI, units; **mmHg** is the universally accepted unit for the measurement of arterial blood pressure as well as other fluid pressures in the body.

Under austere conditions, when electronic measuring devices cannot be used or are lacking, a fluid column of sterile NaCl 0.9% in sterile plastic tubing can be used to measure mean invasive pressure in central intrathoracic veins and even in arteries as *cmH_2O*. The specific weight of NaCl 0.9% is almost identical to that of pure water (less than 0.5% heavier) and there is a slight expansion of the volume of water from 4°C (the standard for comparisons between H_2O and mmHg) to room temperature. The error introduced by using standard conversions from cmH_2O to mmHg (fig A-1) under such circumstances is without clinical importance. A mean arterial pressure (MAP) balancing a 100 cm column of NaCl 0.9% equals 75 mmHg, an 80 cm column equals 60 mmHg and a 10 cm column equals 7.5 mmHg (see Table A-5 for other conversion examples).

The relationship between hydrostatic pressures, flow, fluid viscosity, and resistance.

When a fluid flows through a tube or a system of tubes, the pressure measured at the outlet is reduced compared to the pressure at the inlet. The difference between inlet and outlet pressures, the ΔP or *driving pressure*, is determined by the *resistance to flow,* **R,** through the tube system. The relationship between Δ**P**, flow (**Q**), and **R** is written

$$\frac{\Delta \mathbf{P}}{\mathbf{Q}} = \mathbf{R}$$

The **R** is mainly determined by

- The diameter (radius x 2) and length (l) of the tubing.
- The rate of flow (Q) through the system.
- The viscosity ($\boldsymbol{\eta}$ $-$ eta) of the fluid flowing through the system. Viscosity is usually measured in centipoise (**cP**), viscosity of blood and plasma may also be given *relative* to water, where the value for water is set to 1. The viscosity of a fluid is reduced by *increases* both in the fluid *temperature* and in the *flow rate* (i.e. increased cardiac output reduces the viscosity of blood).

If the fluid flow through a cylindrical pipe is laminar, the relationship between the factors can be expressed by **Poiseuille's law**, which states that

$$\frac{\mathbf{8\ x\ fluid\ viscosity\ x\ tube\ length}}{\boldsymbol{\pi}\ \mathbf{x\ tube\ radius^4}} = \mathbf{Resistance}$$

or, using the corresponding symbols:

$$\frac{\mathbf{8\ x\ \eta\ x\ l}}{\boldsymbol{\pi}\ \mathbf{x\ r^4}} = \mathbf{R}$$

Although strictly speaking valid only for an ideal fluid and linear flow, this equation is also used to illustrate the *effect of changes in airway radius on the pressure-flow relations of air (*or other gas mixtures) during ventilation.

In the vascular bed, the *resistance* (**R**) is calculated as the net forward pressure divided by the blood flow. For the systemic vascular bed, the net forward pressure is the middle arterial pressure (**MAP**) minus the right atrial pressure (usually substituted by the central venous pressure (**CVP**)). The global flow is the cardiac output (**C.O.**); the equation for systemic vascular resistance (**SVR)** then becomes

$$\frac{\mathbf{MAP - CVP}}{\mathbf{C.O.}} = \mathbf{SVR}$$

(see also Part 3-1, an overview of hemodynamic parameters and equations is presented in Table 3-1). In this equation, the effect of blood viscosity is included in the expression for resistance. When the concentration of erythrocytes (the hematocrit) changes, the blood viscosity (and thus also the calculated resistance) also change. There is a close to linear relationship between hematocrit and the hemoglobin concentration in normal blood (10), the viscosity thus varies with the Hb levels in a similar way. The relationship between Hb and viscosity is non-linear; for levels representing anemia, however, they are close to linear. The resistance to ejection of the cardiac stroke volume is reduced by a decrease in blood viscosity, greatly facilitating the increase in C.O. during anemia. In animal experiments, a close to 100% increase of C.O. in response to a 60% Hb reduction was reduced to about 40% if the loss of blood was substituted by a fluid with high viscosity instead of a fluid with low viscosity (11).

Vascular resistance units. Both SVR and PVR is usually given in the unit *dyn x sec x cm^{-5}* – a unit derived from the SI system. If we insert the measured pressures in *mmHg*, and the C.O. in *liters/min*, into the equation above, we can convert this result to the unit *dyn x sec x cm^{-5}* by multiplying the result with 80 (or, more accurately, 79.9).

Calculation of body surface area (BSA) and indexing of the C.O.

The C.O. of a small person is generally lower than that of a person with a larger body mass, the calculated vascular resistance of a smaller person will then be higher than in a bigger person if

the same pressures are measured in both. It is therefore common to correct for this by using the *indexed cardiac output* (CI, the measured C.O. divided by the body surface area – **BSA,** in m^2), both for comparisons of the cardiac output *per se* and when calculating the vascular resistance. Several methods for calculations of BSA exist; the equation of DuBois (12) is the most commonly used, while that of Mosteller (13) is simple to calculate (for both: Weight (W) is given in Kg, Height (H) in cm).

$$\mathbf{BSA}\ (\boldsymbol{m^2}) = \mathbf{0.007184} \times \left[\mathbf{W^{0.425}} \times \mathbf{H^{0.725}}\right] \quad \textit{DuBois equation}$$

$$\mathbf{BSA}\ (\boldsymbol{m^2}) = \sqrt{\frac{\mathbf{H \times W}}{\mathbf{3600}}} \quad \textit{Mosteller equation}$$

To give a simple reference value, a person with a weight of 80 kg and a height of 180 cm has a BSA of about 2 m^2 and the CI is half of the measured C.O. (CI l/min/m^2=C.O. l/min/2m^2).

Not only the dimensions of the arterial vascular bed *per se* but also blood viscosity, vascular elasticity, and reflected pressure waves contribute to the force that opposes the ejection of blood from the left ventricle during systole (see Part 3-1). The expression *vascular impedance* is sometimes used as a measure of the sum of these forces (14). V*ascular conductance* measures the ability of blood vessels to accommodate a flow increase (15); these two terms are often used within the field of cardiology and circulatory research.

Osmotic pressure.

The molecules in a fluid are in constant movement. When molecules in a solution encounter a physical or biological membrane that has microscopic holes or pores (a *semi-permeable* membrane), the molecules that encounter such pores on contact with the membrane will pass through if the pore is larger than the molecule. If they encounter an area of the membrane *between* pores, they will rebound. A semi-permeable membrane is usually freely permeable to water molecules; the pore size determines to which extent other types of molecules or ions can pass through, or be reflected when a pore is encountered.

In this connection, molecules and ions that do not pass freely through the pores but rebound because of their size (or other properties) are denoted as *osmoles.* Their concentration is measured in *osmoles per liter (Osm/l)*; within the human organism, concentrations are usually given in *milliosmoles per liter (mOsm/l).* For non-dissociated molecules, the mole- and osmole concentration is the same, for molecules like NaCl that dissociate completely in water, each mmole of NaCl becomes two mOsm (Na^+ *plus* Cl^-).

If the fluid on one side of a semipermeable membrane contains pure water, and the water on the other side contains osmotically active solutes that do not pass through the pores, more water molecules will pass from the side of pure water to the one containing solutes than the opposite. The volume of fluid on the side containing the solutes consequently increases, and *vice versa* on the other side. The same phenomenon will occur if the fluid on both sides of the membrane contains osmoles but in different concentrations. This process continues until an increased counter pressure from the solute side of the membrane force an equal number of H_2O molecules to pass through the membrane from each side during each unit of time. If the semipermeable membrane is positioned in a tube connecting two vertical tubes containing the two different fluids, the volume increase on the side containing osmoles (or a higher concentration of osmoles than the other side) results in a higher column of fluid on the solute side. The difference in fluid column height on the two sides represents the force necessary to obtain an equilibrium between

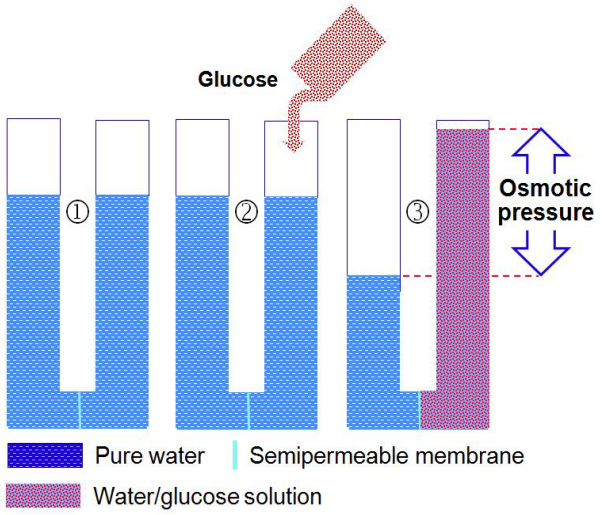

Figure A-3: Osmotic pressure.
① Equilibrium on both sides of a semipermeable membrane. ② Addition of glucose on one side. ③ Creation of an osmotic pressure after the glucose has dissolved in water.

the passage of water molecules from each side of the membrane (fig A-3) to the other. The hydrostatic pressure (usually measured in mmHg, see above) is measured as the difference in column heights and represents *the osmotic pressure* created by the difference in the number of osmoles in the solutions on each side of the membrane. The potential force of the osmotic difference is illustrated by the fact that dissolving a mole (see above) of any solute that cannot pass through the membrane pores in water to a final volume of one liter, creates an osmotic pressure equal to about 22.4 atmospheres, *or* a column of water about 225 meters high (16).

In the human organism, all fluids consist of water in which various types of molecules and ions are dissolved. The fluid compartments of the body are separated by biological semipermeable membranes; these are, however, more complex than inert physical membranes. Cell membranes contain protein channels called aquaporins (17) which are freely permeable to water. Permeability to molecules and ions is, however, regulated by various specialized proteins for ion exchange and transport of molecules; different cell types have different properties as to the permeability to water molecules, ions, and other molecules.

The water balance between the intracellular and extracellular compartments is *partly* determined by the concentration of solutes on each side, this effect is modified by the properties and efficiency of the transport proteins residing in the cell membranes of each particular type of cell. The transport proteins of the cell membrane are energy-dependent; their activity becomes diminished or abolished if the cells are unable to maintain sufficient energy production (e.g. during anoxia). Under such conditions, an imbalance between the concentration of osmoles inside and outside cells will rapidly change the cell volume.

Cells may *shrink* if the extracellular osmotic pressure increases rapidly without a similar increase intracellularly, or *increase* their volume (intracellular edema) during a rapid decrease in extracellular osmotic pressures *or* increases in osmotic intracellular pressure, *or* both.

The **osmotic activity** of a solution is given either as it's

- *Osmolarity*: The amount of osmotically active solutes *per liter* of solvent, the volume is measured *after* the addition of the solutes, *or*
- *Osmolality*: The amount of osmotically active solutes *per kg* of solvent weighed *before the* addition of the solutes.

In the aquatic fluids within the human body, the difference between the two methods is small; for practical analytical reasons, the latter unit is the one commonly measured in clinical biochemical laboratories today. The normal range is 275-310 mOsm/kg.

Osmolarity and the osmolar gap.

Under normal circumstances, the substances that create most of the osmotic pressure in the extracellular fluid, including plasma, are the *major electrolytes, glucose, and urea*. The sum of electrolytes (anions and cations) is usually calculated as the millimolar (or mEq) concentration of sodium, [Na^+], x 2, the equation for calculating the osmolality in the blood is then

(Na^+ mmol/l x 2*) + Glucose (mmol/l) + Urea (mmol/l).

**The constant 1.86 is also commonly used instead of 2 but does not result in better accuracy* (18).

If glucose and urea concentrations are given as mg/dl, the glucose value is divided by 18 and the urea value by 2.8, see table A-1.

An increased quantity of osmotically active molecules (increased osmolarity) intracellularly may arise following events such as ischemic damage to cells, in which large intracellular molecules break down into several smaller fragments. Since ion exchangers and water pumps of the cell membrane are energy-dependent, they also cease to function, and fluid is transported *into* the cells by the increased intracellular osmolarity, creating *intracellular edema*. The same imbalance, with the formation of intracellular edema, occurs if the number of osmotically active molecules in extracellular fluid rapidly declines. This may occur in circumstances such as acute hyponatremia (water intoxication) or during a rapid drop in glucose concentration after a slow but substantial increase (e.g. too rapid correction of blood glucose levels when insulin is given to hyperglycemic patients).

On the other hand, an increase in osmolarity in the extracellular fluid (hyperglycemia, hypernatremia, and rise in urea) will draw water *out* of the cells, making them shrink. This principle is the basis for the treatment of cerebral edema with hyperosmolar solutions (mannitol, hypertonic NaCl), it is still unclear which of these alternatives is better (19, 20). On the other hand, both acute hyper- and hyponatremia can cause brain damage (21). If such changes arise slowly, however, the difference in intracellular and extracellular osmolality remains moderate. Sudden changes in plasma osmolarity due to rapid infusions of hyper- or hypo-osmolar fluids may affect organ function, changes in cerebral function are especially common under such circumstances.

The Osmolar gap. Not all types of endogenous or exogenous molecules exerting an osmolar force in the body fluids are measured routinely. A difference between the *calculated* and *measured* osmolality in a blood sample is called an *osmolar gap*; an increased gap indicates the presence of *non-measured osmoles* like *ethanol, methanol, mannitol* or others in the blood. Such gap calculations show a considerable variation, the specificity of gaps below 20 mOsm/l for the detection of exogenous molecules is uncertain (18, 22).

Colloid osmotic (oncotic) pressure.

In medicine, the colloid osmotic pressure can be seen as a special type of osmotic pressure where the semipermeable membrane is created by structures in the capillary wall (fig A-4). These structures have properties comparable to a membrane with large pores, the capillary wall is freely permeable to water and smaller solutes like ions and molecules of low molecular weight, but only partly (and slowly) permeable to plasma proteins. Of these, albumin molecules are the most numerous and have the largest effect. The oncotic pressure is usually measured in mmHg; in health, with normal concentrations of plasma proteins, the total oncotic pressure in plasma is calculated to be in the 25-28 mmHg range. Albumin contributes close to 80% of the total effect.

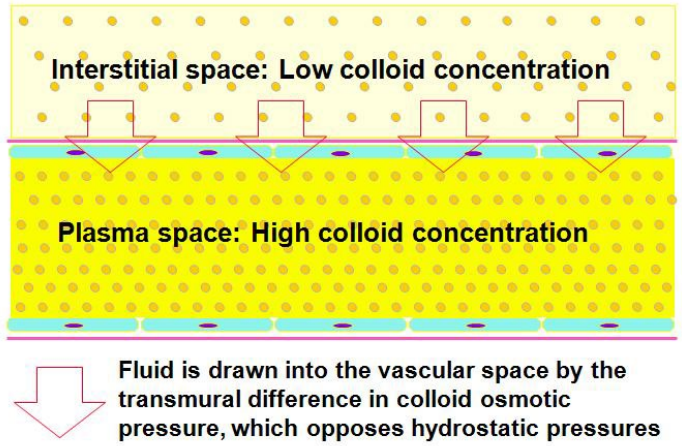

Figure A-4: *Colloid osmotic pressure across the capillary wall.*

One gram/l of albumin exerts an oncotic pressure of approx. 5.5 mmHg while one gram/l of globulins exerts a pressure of 1.4 mmHg (16).

The permeability of the capillary wall varies between different organs; in most areas of the body it is readily permeable to electrolytes, glucose, and urea, but only partly permeable to proteins. The capillaries in the cerebral circulation are much less permeable than those in other tissues, creating the so-called *blood-brain barrier*. The concentration of proteins in plasma is normally larger than that in the interstitial fluid outside the capillary wall (for oncotic active albumin 1: 2-2.5 (23)); this net oncotic pressure opposes the hydrostatic pressure inside the capillaries and reduces the seepage of plasma fluid to the extravascular compartment (see also Part 2-2). Inflammatory states increase the permeability of the capillary wall; plasma protein leaks from plasma into the interstitial fluid and most of the colloid osmotic force of the blood is lost. The result of this is increased loss of fluid from the intravascular to the interstitial space, resulting in hypovolemia and the formation of interstitial edema.

PROPERTIES OF GASES: INTERACTION BETWEEN PRESSURE, VOLUME, AND TEMPERATURE

At a constant volume, the pressure of a gas increases proportionally to an increase in temperature when the temperature is measured in degrees Kelvin (°K) (i.e. intervals as in °C, but a scale with zero at minus 273°C; 0°C = 273°K, and 37°C = 310°K).

The *volume* of a gas sample containing a given number of molecules changes with both pressure and temperature. The volume is inversely proportional to pressure (doubling the pressure halves the volume, *Boyle's law*) and proportional to temperature changes (when measured in degrees Kelvin, *Gay-Lussac's law*). The consequence of the latter is that a gas sample containing a given number of molecules has a larger volume when measured at body temperature than when measured at room temperature or at 0°C (see above).

The pressure exerted by any gas is proportional to

- The *number of gas molecules* per unit of volume (the density of the gas)
- The *kinetic energy of the gas molecules* (determined by the gas temperature)

The laws above are combined into the general or "**Ideal gas law**". In a sample of gas containing a given number of molecules, the **Pressure (P) x volume (V)** divided by **gas temperature (T)** (*in °Kelvin*) has a constant value, **k**, and can be written as

$$\frac{\mathbf{P \times V}}{\mathbf{T_{(°K)}}} = \boldsymbol{k}$$

If the volume of a gas is kept constant, heating will increase the gas pressure while cooling will reduce it. If the volume of the gas is expanded without adding new gas molecules, the density

of the gas will decrease and the gas pressure will fall. If the gas is compressed, there will be more molecules per unit of volume, and the gas pressure will increase. If the pressure becomes high enough, the gas may turn into a liquid phase if the temperature is not too high (below the *critical temperature*, which has a different value for individual gases). The laws stated above are valid for ideal gases; the deviations exhibited by individual gases are, however, moderate, and the gas laws are assumed to be valid for types of gas and the temperature range of interest in clinical medicine.

Vapor is defined as a substance in the gas phase at a temperature lower than its critical temperature. In everyday nomenclature, we tend to call a gas a vapor if the gas phase coexists in equilibrium with the liquid phase at normal room temperatures (we usually say "water vapor" and not "H_2O gas"). On the other hand, if the boiling point of the substance is below the ambient temperature, leaving no liquid phase, it is called a gas. The semantic difference between gas and vapor has little practical consequence; both behave in accordance with the gas laws below, as long as the individual vapor molecules do not coalesce into aerosol droplets.

Gas volumes measured at body temperature (see above) are usually denoted **BTPS** (**B**ody **T**emperature, ambient **P**ressure, and **S**aturated with water vapor). At room temperature; the volumes are given as **ATPS** (**A**mbient **T**emperature and **P**ressure, **S**aturated with water vapor) together with the actual temperature. If the room temperature was 20°C and the gas was chemically desiccated before entering the reservoir bag, it can be given as **NTP** (**N**ormal **T**emperature, i.e. 20°C, and **P**ressure).

For comparisons of gas volumes measured at different temperatures, volumes are usually recalculated to the volume in a *standardized state*; i.e. what the volume would be if the gas was measured without moisture at 0°C (32°F or 273°K) and a pressure of one atmosphere (**STPD,** see above). When metabolic calculations involving volumes of gases are carried out, gas volumes are given as STPD volumes unless otherwise indicated.

Gas pressures and concentration of gas molecules.

In opposition to the hydrostatic pressures commonly measured in medicine, *gas pressures* are usually measured as *absolute pressure*. An exception to this practice is gas pressures within the airways, which usually are measured in cmH_2O *relative to* ambient pressure. A peak airway pressure delivered by a ventilator during positive pressure ventilation may be around 30 cm H_2O, which is roughly 3% of the atmospheric pressure. The increase in alveolar PO_2 at end inspiration is therefore negligible and usually ignored. A gas may consist of only *one* molecule type (e.g. only O_2 in *pure oxygen*) or be a *mixture* of different molecules (air contains chiefly O_2 and N_2, but also water vapor and small quantities of many other gases).

In space, there are few gas molecules and a low temperature, and the gas pressure is close to zero. In the earth's atmosphere, there are few molecules in the upper regions but the number increases towards the surface of the Earth. At any altitude, the gas pressure in the ambient air represents the combined weight of all types of gas molecules (mainly O_2 and N_2 molecules) above; at sea level, this pressure is defined as one atmosphere (1 Atm).

The individual molecules of any gas (e.g. O_2 or N_2 molecules) are constantly in spontaneous movement (known as *Brownian motion*). These movements are random and in all directions; any surface that is in contact with gas is exposed to a continuous bombardment of gas molecules. In a gas mixture, the pressure of each gas corresponds to the number of molecules of this gas.

If 10% of the molecules in the mixture represents gas X, the pressure of this gas constitutes 10% of the total gas pressure.

The intensity of spontaneous movement increase with increasing temperature and *vice versa*; at absolute zero (0°K, or -273°C) the spontaneous movement of gas molecules ceases. Above this temperature, the bombardment of gas molecules exerts a certain pressure; the *gas pressure* is proportional to the *density of the gas molecules* and the *intensity of their movement*. In a gas mixture, each gas exerts a pressure proportional to its fraction of the total volume (but not to its weight, see Avogadro's law above). Where there is a channel of communication between gas volumes, gas under higher pressure will always flow towards areas where the gas pressure is lower, equalizing the gas pressure.

Units for measurement of gas pressure.

Several different units are in common use within different fields of the natural sciences (e.g. physics, engineering, meteorology, and environmental sciences). In medicine, most of the world uses the unit *kilopascal* **(kPa)** for the measurement of pressures of a gas as such and of gases dissolved in a fluid. In the USA, gas pressures are still measured in *millimeters of mercury* (**mmHg**, or sometimes **Torr** after Torricelli; the difference between the latter two units is too small to be of interest within the field of medicine). See table A-5 for conversion between units of pressure.

From a clinical bedside perspective, the practical advantage of using kPa to measure gas pressures is that the *pressure in kPa* and the *percentage of the gas volume* in a gas mixture have *almost equal* values at sea level (fig. A-1). As the mean atmospheric pressure at sea level is 101.3 kPa, a normal P_aCO_2 of 5.3 kPa corresponds to 5.14%, making it easy to compare the CO_2 concentration in arterial blood (in *kPa*) and in end-expiratory gas (in volume *percent*). Gas pressures within the **airways,** between the two blades of **pleurae**, and in **ventilator tubing** are, however, traditionally *measured in* **cmH_2O**; settings, as well as pressure measurements on most modern ventilators, still use cmH_2O as the common unit of airway pressure. When central venous pressure (CVP) under austere conditions is measured with the aid of a column of sterile, isotonic saline, the pressure is also measured in cmH_2O.

Other common units of pressure encountered *outside the medical profession* are
Bar (which is *almost* equal to atmosphere) and **psi** (pound per square inch):
1 bar = 0.98692 Atm =100 kPa = 750 mm Hg =1000 cm $H_2O \approx 14.5$ psi.
1 psi = 0.0689 bar ≈ 6.89 kPa = 51.7 mm Hg = 70 cm H_2O.
The unit **ATA** (Atmosphere Absolute, *or* absolute atmospheric pressure) is mostly used in connection with diving. It also denotes pressures measured in equivalents to Atm and indicates the total pressure (e.g. atmosphere pressure + water pressure during diving); i.e. at a water depth of 10.13 m, the pressure is increased to 2 ATA.

The concentration of an individual gas in the gas mixture may also be given as a proportion or **fraction (F)** of the total gas content; 50% O_2 in the inspired gas is often expressed as the **inspiratory fraction of O_2** (**F_iO_2**) = 0.5. The fraction multiplied by the ambient atmospheric pressure at the actual elevation or depth gives the pressure of the gas in question (see Part 4-1).

Other units used to quantify gas concentrations.

Within the fields of toxicology and public health, the units **ppm** (parts per million, $1{:}10^6$) or **ppb** (parts per billion, $1{:}10^9$) are commonly used to indicate the concentration of gases with toxic or negative health effects present at very low concentrations. One ppm of the gas X means that for every million molecules in a gas mixture, one will be an X molecule; the concentration of a gas representing 1% of the total volume is equivalent to 10 000 ppm. In meteorology and climatology, amounts of gases (especially CO_2) are often measured in weight units, usually tons. Such calculations are based on gas volumes and the molecular weight of the gas (see moles and Avogadro's number above). As one mole of CO_2 weighs 44 grams and occupies 22.4 liters at STPD, and a resting person weighing around 70 kg produce approximately 0.2 liters of CO_2 at SDPT per minute and 12 l per hour, the person produces a minimum of 288 liters of CO_2 in 24 hours. This amounts to (288 l per 24 h/22.4 l) = 12.86 moles per 24 hours or 566 g/24 hours. As only ⅓ of the time is spent resting (i.e. sleeping) and the CO_2 production during everyday activity is at least 100% higher, the CO_2 production of an ordinary person may be closer to 1 kg/24 hours, or more.

Diffusion and solubility of gases in liquids.

When a gas encounters the surface of a fluid, the spontaneous movements of the gas molecules will cause some of them to *diffuse* into the fluid. At the interface between a gas and a fluid surface and in the first micrometer (1µm) layer beneath, **equilibrium** between the **pressure of the gas above the surface** and the **gas dissolved in the fluid phase** is achieved so rapidly (less than ¼ millisecond (24)) that it can be considered instantaneous (figure A-5). The equilibrium of gas pressures is not, however, the same as an equilibrium between the *number* of molecules in the gas and those dissolved in the fluid; this ratio is defined by the *solubility* of the gas in the actual type of fluid (see below).

If there is no mixing of fluid layers, diffusion of the gas deeper down into the fluid phase is a slow process; the time until equilibration in each successive fluid layer increase proportional to the square value of the distance from the interface (Figure A-6). The speed of diffusion is also determined by the concentration gradient (Fick's law); i.e. the difference in gas pressure between the gas phase and fluid at the interface and between successive layers of fluid.

The **diffusion distance** between capillaries and cells is short and seldom more than 50 µm, for this distance diffusion is completed rapidly. In addition, as there is some seepage of gas-filled fluid out of the capillaries and into the interstitial fluid, *convection* (i.e. transport of molecules as part of a flow of liquid) is therefore also part of the mechanism for O_2 transport to the cells.

The **rate (or speed) of diffusion** varies between different gases; as a general rule, diffusion is fastest for gases with low molecular weight and slows down with increasing weight (*Graham's law* states that the rate of diffusion of a gas is inversely proportional to the square root of the mass of its particles). The molecular weight of the three gases of greatest interest in medicine (O_2, CO_2, and N_2) do not differ greatly (table A-4), consequently, their *speed of diffusion* varies by only about 10%.

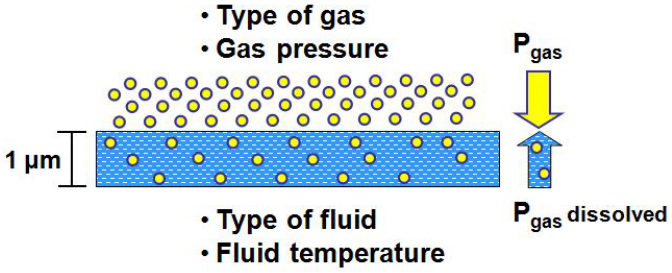

Figure A-5: *Factors important for the amount of gas dissolved in a fluid at the gas-fluid interface.*

When the diffusion process is complete, the **solubility** of a gas in a particular fluid defines the number of gas molecules dissolved in the fluid phase relative to the number in the gas phase at pressure equilibrium. The number of gas molecules that can be dissolved in a fluid is determined by the chemical properties of both gas and fluid molecules; in addition, the pressure of the gas and the temperature of the fluid determine the mass of gas molecules that can be dissolved (fig A-5). If the dissolved gas reacts with, or bind to, molecules suspended in the fluid (e.g. Hb molecules in the blood), more molecules are transferred from the gas into the fluid, but the number of molecules actually dissolved stay the same.

In the human organism, all fluids are aquatic, with various contents of ions, proteins, and nutrients. The **solubility** of various gases in this fluid varies considerably (see below). The number of gas molecules dissolved in the fluid film at the gas-fluid interface is much greater for a highly soluble gas, the number of molecules that penetrate deeper into the fluid phase is therefore much larger than for gas with limited solubility. The gases of main interest in the human organism are O_2, CO_2, and N_2. Even if the body fluids vary somewhat as to the concentration of various electrolytes and molecules, the solubility of gases like O_2 and CO_2 in pure water and plasma differs only modesty. In experiments comparing the solubility of these gases in either pure water, isotonic NaCl, or plasma, the difference in solubility between these fluids was found to be in the 10-15% range (25, 26).

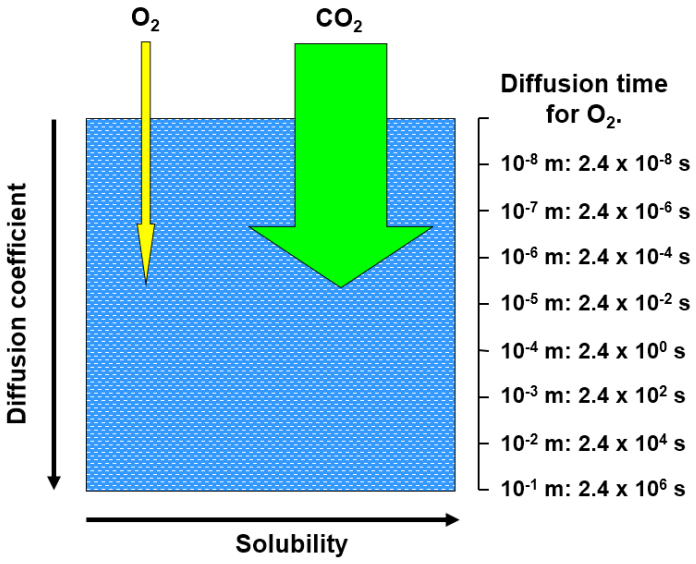

Figure A-6: *Diffusion rates for O_2 and CO_2 are almost equal, but their solubility is very different.*

The number of molecules of a gas *dissolved in a fluid* and exerting a given pressure is different from the number in a *sample of gas* exerting the same pressure. The magnitude of this difference is determined by the solubility of the gas in the fluid. The solubility is usually given as ml gas/ml liquid *or* as mol gas/l liquid at one atmosphere. The *Ostwald coefficient* refers to solubility in ml gas/ml fluid at body temperature, 37°C (or 98.6°F); the *Bunsen coefficient* refers to solubility in ml/ml at 0°C (or 32°F). The solubility of CO_2 in plasma is much higher than that of O_2, the *Ostwald coefficients* at one atmosphere are 0.515 ml gas/ml plasma for CO_2 and 0.0214 ml gas/ml plasma for O_2 (27), i.e. a ratio of 1:24. The solubility of N_2 is close to half of that of O_2 (28), while that of nitrous oxide (N_2O) is only slightly lower than that of CO_2 (0.46 ml gas/ml water at 37°C).

The higher solubility of CO_2 than of the other two gases has led to the common assumption that CO_2 diffuses much faster than O_2; in reality, CO_2 diffuses only slightly faster but the difference in solubility is so high that the amount of CO_2 dissolved in the body fluids is about 20 times that of O_2 (fig A-6).

Transport of gases by the blood (e.g. O_2, CO_2, N_2, anesthetic- and other gases).

The gas exchange always starts with the gas diffusing into and subsequently dissolving in the plasma layer closest to the capillary wall. Oxygen from the alveoli enters the plasma phase of the blood in the pulmonary capillaries; CO_2 produced by the metabolism dissolves in the intracellular fluid and subsequently diffuses out of the cells, passing through a layer of interstitial fluid and into the plasma phase in the tissue capillaries (Part 5-2). For O_2 in the lungs, diffusion into plasma is followed by binding to Hb molecules (as HbO_2); in the tissues, some dissolved CO_2 is bound to Hb as carbamino compounds while the bulk of CO_2 is converted to carbonic acid and bicarbonate inside the erythrocytes.

For both O_2 and CO_2, the amount of gas dissolved in plasma represents only a small part of the total content in the blood. The bulk of O_2 in the blood (95-99% of the total in persons with Hb in the normal range) is bound to hemoglobin; the bulk of CO_2 (85-90% of the total) is transported as bicarbonate. In the tissues, the rate of diffusion and solubility of the gases in aquatic fluids are important parameters determining the transport of gases.

Type of gas. The molecular configuration of the gas has, a large effect (26, 29, 30) on both diffusion rate and solubility; the solubility difference between O_2 and CO_2 dissolved in the same medium is substantial (see above).

Effect of **Gas pressure.** The number of gas molecules dissolved in the fluid is also directly proportional to the pressure of the gas in the gas phase (Henry's law). If the gas is a mixture of several gases, the number of molecules dissolved in the fluid is a function of both the partial pressure of each gas and its solubility.

Effect of **Fluid temperature.** The temperature of the fluid also affects the amount of gas that can be dissolved; more gas molecules dissolve in a fluid at lower temperatures. At 20°C, plasma contains about 53% more dissolved CO_2 than at a body temperature of 37°C (27) while it contains approximately 30% more dissolved O_2.

Gas diffusion/effusion in body fluids.

Both diffusion speed and solubility are important for how quickly gases pass from the alveolar gas into the blood or are removed from the blood via diffusion into the alveoli. They also determine how rapidly equilibrium occurs between the gas pressure of a given gas in the lungs and the blood, and between the blood and various tissues in the various organs.

These factors are important also for the effect of anesthetic gases. Gases with a high speed of diffusion and low solubility in blood will increase the blood concentration (and thus the tissue concentration in the brain) of the gas quickly, and the patient falls asleep and wake up rapidly. Gases with a low speed of diffusion and high solubility will increase the blood concentration of the gas more slowly, and the effect will be less immediate. Following the termination of anesthesia, there will still be a lot of gas dissolved in the intracellular fluid, extravascular fluid, and blood, so the patient will awaken more slowly. For these gases, the degree of binding to tissues will also be an important factor for uptake and elimination dynamics.

ADDITIONAL PHYSIOLOGICAL TOPICS

Transmural and transpulmonary pressure.

A hollow organ (e.g. heart or lungs) or a tube with an elastic wall (e.g. blood vessels) will expand when the pressure inside of the organ or tube increases. However, the pressure on the outside

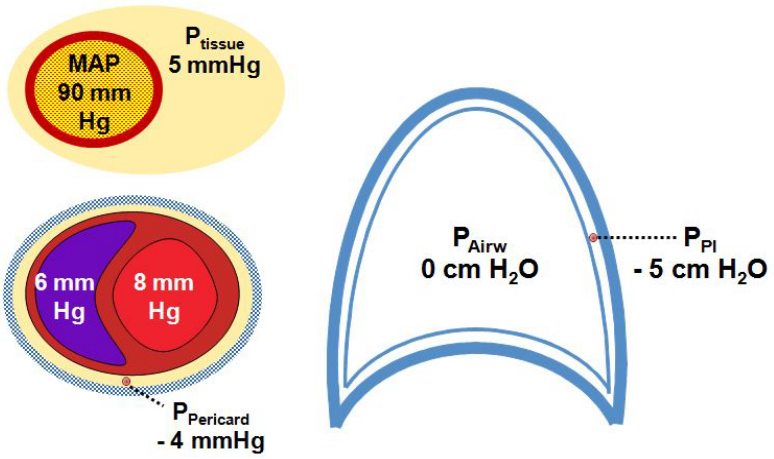

Figure A-7: *Examples of transpulmonary and transmural pressures.*

of the hollow organ or vessel may also vary, and may be higher or lower than atmospheric pressure (Figure A-7). The *effective* distending pressure affecting the organ is determined by the *difference* in pressure between the inside and the outside. This *net distending pressure* (e.g. the pressure inside the heart *minus* pressure outside the heart, or the pressure inside the lungs *minus* pressure in the pleural space) is usually referred to as *transmural*, *transcardiac-* or *transpulmonary pressure*, respectively (fig A-7).

If the pressure on the outside is constant, changes in *pressure on the inside* will produce a corresponding change in transmural pressure. If the pressure on the inside is constant, changes in *pressure on the outside* will also produce a corresponding change in transmural pressure. These conditions are of great importance for the relationship between a filling pressure *measured inside the organ* (which are measured relative to ambient pressure) and the *effective* filling pressure (the *net* expanding pressure) inside the heart. The relationship between measured blood pressure and effective perfusion pressure in different organs varies, especially when tissue edema or other compressive forces increase the pressure surrounding the vasculature.

Elasticity and compliance.

Elasticity means that an object (e.g. elastic band, elastic tissue structures) that is subjected to a particular force changes its shape, and then returns to its previous shape when this force ceases to operate.

Compliance of a hollow organ is the relationship between a given increase in the volume of the organ and the increase in transmural pressure that is necessary to produce this increase in volume.

$$\frac{\Delta \mathbf{Volume}}{\Delta \mathbf{Pressure}} = \mathbf{Compliance}$$

The compliance of organs change with increasing volume; as the fibers of the connecting tissue are stretched, higher pressures are necessary to increase the volume further. In the chambers of the heart, the end-diastolic filling volume in the lower or normal range is largely determined by the net (transmural) filling pressures. A change in the compliance of the myocardium will, however, change the relationship between filling pressure and filling volume. Such changes are common in disease and increase with age; individual variations between younger and healthy persons also exist. As compliance changes may be difficult to quantify precisely at the bedside, deductions about net filling volumes (preload) from measurements of filling pressures may lead to erroneous results (see also Part 3-1).

Pulmonary compliance is measured as the relationship between the increase in pulmonary gas volume and the corresponding increase in pulmonary transpulmonary pressure. Correct measurement assumes that the pressure is measured after the gas volume is distributed evenly within the lungs (*static compliance*). Exact measurements of intrapleural pressure (Part 4-1) are difficult to perform in a clinical setting. In clinical practice, lung compliance is often measured in patients on ventilators by inflating the lungs with a predetermined volume and recording the airway pressure increase after an appropriate inspiratory pause, when the gas can be assumed to be evenly distributed. For example; if the lungs are insufflated with 1000 ml of gas and the increase in airway pressure is measured to 10 cmH_2O after the gas is evenly distributed (i.e. stable airway pressure), the compliance of the lungs is 1000 ml/10 cmH_2O = 100 ml/cm H_2O (fig A-8).

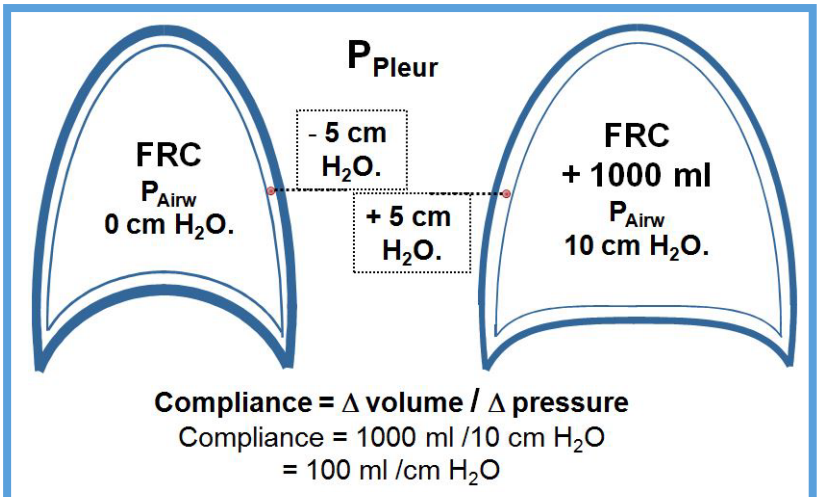

Figure A-8: *Airway and pleural pressures are necessary for accurate calculation of compliance of the lungs.*

This method does not, however, measure only the compliance of the lung tissue itself, but also the effect of structures *surrounding* the lung. Primarily, the rigidity of the thoracic wall (which may increase dramatically, e.g. in circumferential burns) and pressure from abdominal organs and fat will affect the final pressure increase. In addition, any accumulations of intrapleural fluid, connective tissue, clotted hematomas, or air in the space between the pleurae and under the diaphragm are important causes of error. Therefore, the *exact* measurement of the true compliance of the lungs (i.e. the true transpulmonary pressure) in clinical settings is difficult. Measurements of the esophageal pressure utilizing a soft balloon catheter represent an approximation to the pleural pressure and are sometimes used to estimate the trans-pulmonary pressure with the intent of optimizing ventilator settings (reviewed in ref. 31).

Measurement of so-called *dynamic compliance* (i.e. the pressure that is generated in the major airways when lungs are rapidly insufflated) is an imprecise method that introduces substantial errors when the airway resistance is increased. Comparison between dynamic and static compliance may, however, impart information about the importance of airway resistance in an individual patient.

Adhesion between smooth surfaces – the capillary force.

If two surface-ground plates of glass or other non-magnetic material are held in contact when dry, they show no tendency to adhere to each other. However, if the air between the plates is replaced with a thin layer of fluid, they will still easily move against each other in the lateral plane. They are, however, almost impossible to part by the use of a perpendicular force, a mechanism called the capillary action or capillary force.

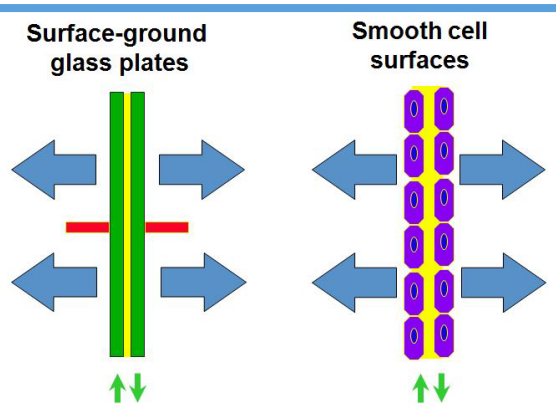

Figure A-9: *Smooth surfaces covered by a thin layer of fluid slide easily against each other in the longitudinal plane, but cannot be separated by a perpendicular force.*

The layers of cells covering the surface of the two pleurae in the lungs and thoracic cage also form plane surfaces, and these too have a thin layer of fluid between them. This enables the pleural surfaces to move more or less freely against each other in the lateral plane, while the contact between them is impossible to break in a plane perpendicular to the surface. This effect "glues" the lungs firmly to the inside of the thoracic cavity and the upper surface of the diaphragm (Fig A-9). If air enters the space between the pleurae so that the fluid film is broken (pneumothorax), the strong adhesion between the pleurae becomes defective, causing the lungs to collapse partly or completely (see also Part 4-3).

Surface tension and surfactant effect – the surface force of a bubble.

A fluid film has a certain surface tension; a fluid bubble will try to contract and diminish its volume if unopposed. An inflated soap bubble is a good example of this: if insufflated on the end of a spindle, the bubble will rapidly shrink and collapse if the air is allowed to flow out freely. The pressure (**P**) inside such a bubble depends on the surface tension (**T**) of the fluid film and the radius (**r**) of the bubble; the equation describing this relationship is written

$$\frac{2T}{r} = P$$

From this equation, it can be concluded that the pressure inside a small bubble will be greater than in a large one. If there is free communication between the bubbles, a smaller bubble will therefore empty itself into the large one (Fig A-10).

The surface of the alveoli is covered by a thin layer of fluid which functions in the same way as a fluid bubble; the surface tension of this fluid is trying to make the bubble (and the alveolus) contract. Since small fluid bubbles will have a greater tendency to contract than large ones, we would expect that those small alveoli would constantly empty themselves into larger ones and then collapse (alveolar areas that have collapsed and do not contain gas are re-ferred to as *atelectasis* – see also Part 4-3).

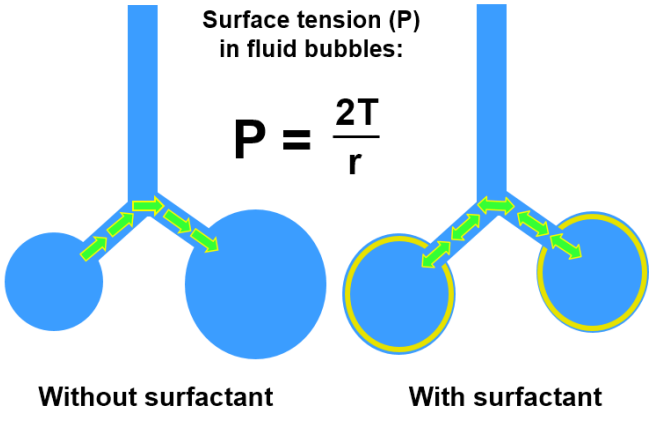

Figure A-10: *Surfactant counteracts the effect of fluid surface tension in the alveoli.*

The reason why this does not occur under normal conditions is that some of the endothelial airway cells (type II alveolar cells, see Part 4-1) produce a substance (a phospholipid) called *surfactant.* When this phospholipid is part of the fluid lining the alveoli, it reduces the surface tension of the fluid. The effect of surfactant is small when the alveolar diameter is great and the surfactant film is thin. When the

alveolar diameter decreases, the film becomes thicker, and the effect of the surfactant increases. In this way, surfactant reduces the tendency of small alveoli to collapse and form atelectasis (Part 4-2, shunt mechanisms). Surfactant *deficiency* may cause widespread atelectasis and lung failure, it is most common in premature babies (32), but may also occur in adults suffering from serious respiratory failure (e.g. ARDS (33), see also Part 4-3.

kPa	% at 1 atm	mmHg, Torr	cmH_2O	F_{atm}	bar
1.0	0.99	7.5	10	0.0099	0.01
2.0	1.97	15	20	0.0197	0.02
3.0	2.96	22.5	30	0.0296	0.03
4.0	3.95	30	40	0.0395	0.04
5.0	4.94	37.5	50	0.0494	0.05
5.3	5.23	40	53	0.0523	0.053
6.0	5.92	45	60	0.0592	0.06
6.3	6.22	47	63	0.0622	0.063
7.0	6.91	52.5	70	0.0691	0.07
8.0	7.90	60	80	0.0790	0.08
9.0	8.88	67.5	90	0.0888	0.09
10.0	9.87	75	100	0.0987	0.1
11.0	10.86	82.5	110	0.1086	0.11
12.0	11.85	90	120	0.1185	0.12
13.0	12.83	97.5	130	0.1283	0.13
13.3	13.13	100	133	0.1313	0.133
14.0	13.82	105	140	0.1382	0.14
15.0	14.81	112.5	150	0.1481	0.15
16.0	15.79	120	160	0.1579	0.16
17.0	16.78	127.5	170	0.1678	0.17
18.0	17.77	135	180	0.1777	0.18
19.0	18.76	142.5	190	0.1876	0.19
20.0	19.74	150	200	0.1974	0.2
21.2	20.93	159.0	212	0.2093	0.212
30.0	29.62	225	300	0.2962	0.3
40.0	39.49	300	400	0.3949	0.4
50.0	49.36	375	500	0.4936	0.5
60.0	59.23	450	600	0.5923	0.6
70.0	69.10	525	700	0.6910	0.7
80.0	78.97	600	800	0.7897	0.8
90.0	88.85	675	900	0.8885	0.9
101.3	100.00	760	1013	1.0000	1.013

Table A-5: **Comparison of units used for pressure measurement.** *Values of special interest in medicine* (e.g. P_aCO_2 and P_VO_2, P_{H_2O}, P_aO_2, normal ambient PO_2, theoretical maximal P_AO_2) *are shown with coloured background.* F_{atm} *= fraction of one atmosphere.*

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