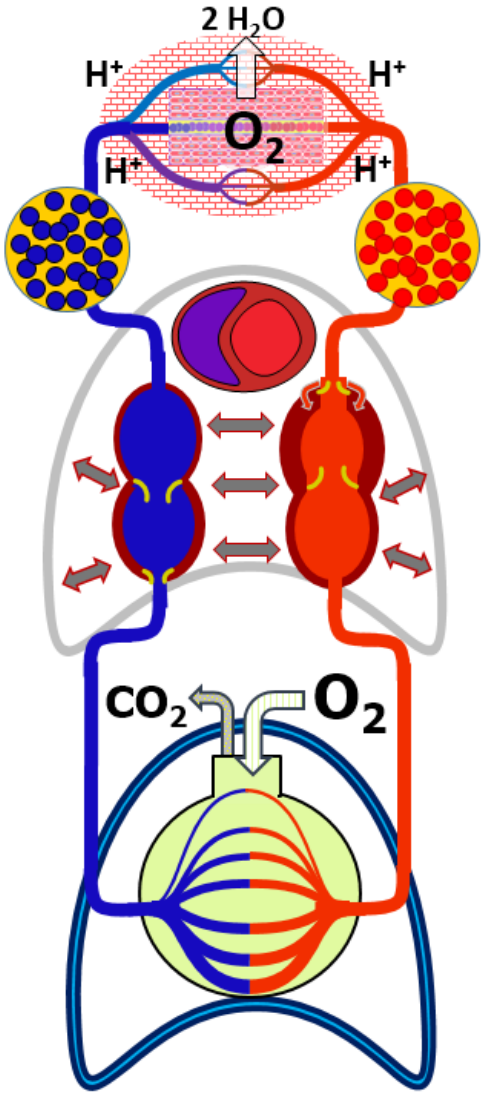

OXYGEN DELIVERY, CONSUMPTION AND OXYGENATION FAILURE.

THE BASIC COMPONENTS

A SLIDESHOW

COMPANION

TO

THE O_2 COMPENDIUM

HELGE OPDAHL MD, PhD

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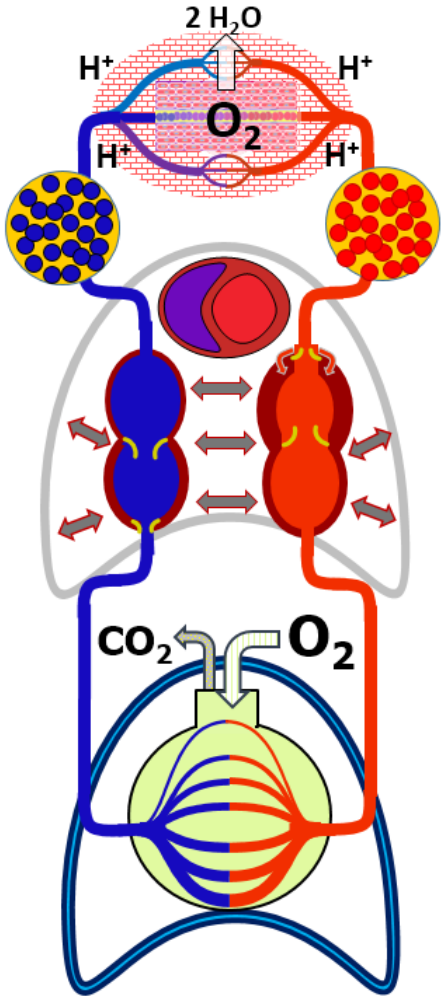

This presentation consists of

- Two flowcharts displaying the factors involved in tissue oxygenation and oxygenation failure.
- Text slides containing definitions of the factors and description of their importance.
- Graphic displays of O_2 distribution and delivery.

How to use this presentation:

- Clicking on the factors within bold frames in the flows chart jumps to text slide(s) with more information and the role of each factor.
- Navigate back and forth by scrolling, clicking on the pictures or on the buttons at the bottom.

Blue numbers in italics (e.g. *59, 68*) refers to *pages* in **The O_2 Compendium** containing more details and explanations. To access the appropriate page, open the Compendium window and enter *Shift-Control-N* and *page number*.

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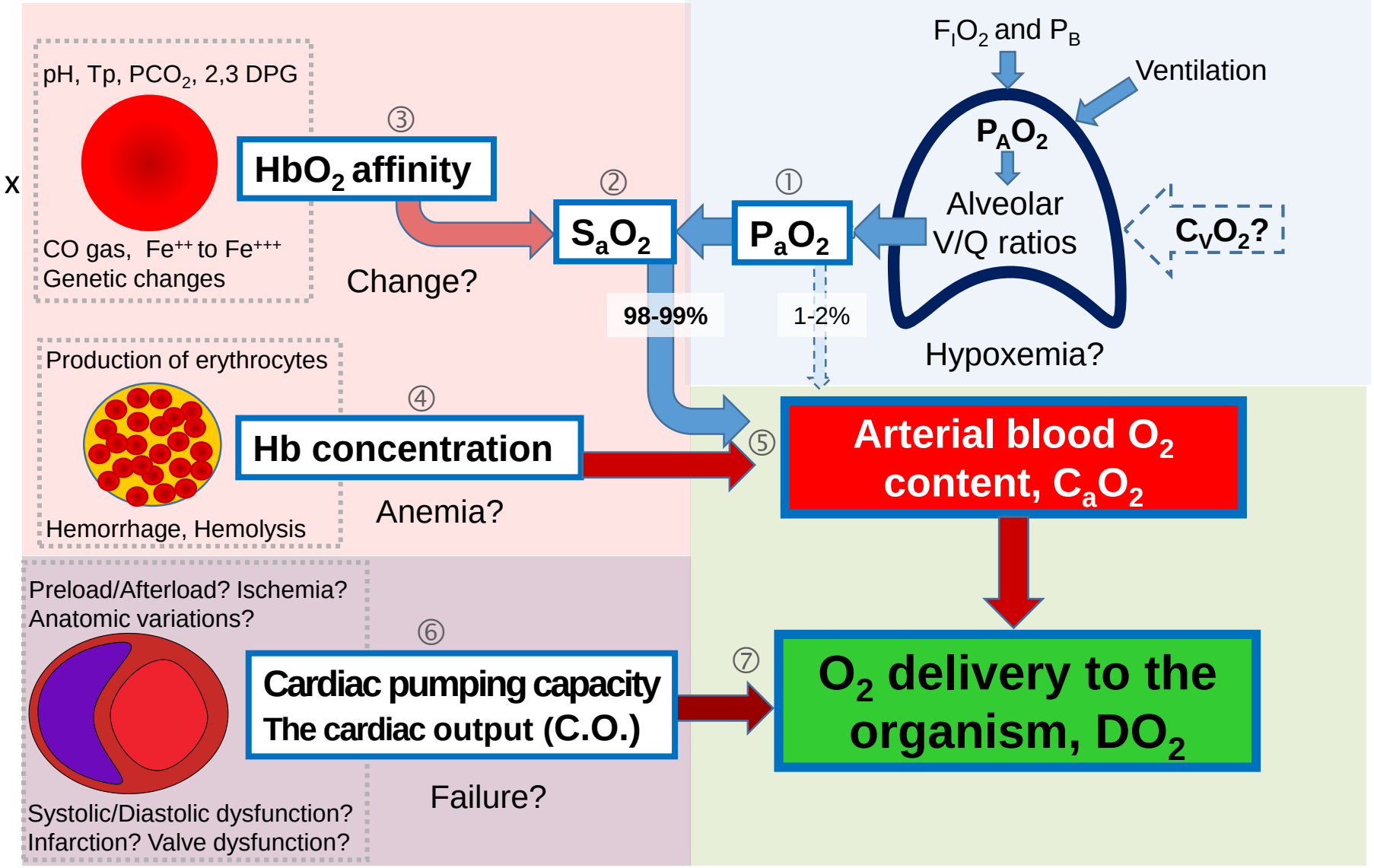
To flowchart 1

OXYGEN SUPPLY TO THE ORGANISM

④ ⑤ ⑥ ⑦ ⑧ ⑩



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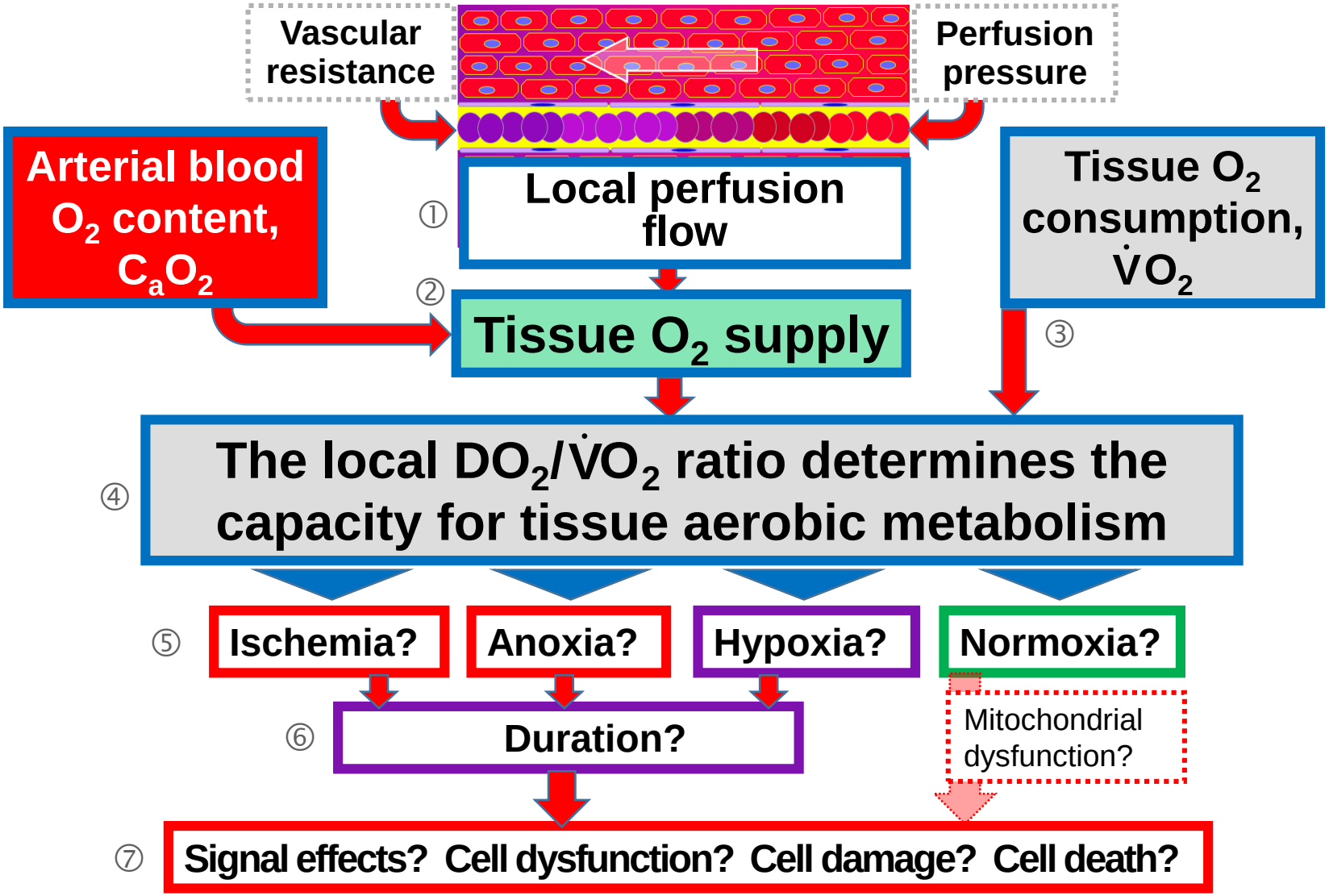
Next slide: Flowchart 2

- AND TISSUE OXYGEN SUPPLY



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P_aO_2, the arterial oxygen gas pressure *(4 slides)*

The P_aO_2 is the pressure exerted by O_2 gas molecules dissolved in the fluid phase (i.e. plasma and intraerythrocyte fluid) of arterial blood. It is linearly proportional to the quantity of dissolved O_2. In persons with **normal lung function,** the P_aO_2 is *close to identical* to the mean alveolar PO_2 ($\mathbf{P_AO_2}$) regardless of the venous O_2 content. The $\mathbf{P_AO_2}$ is determined by

- The fraction ($\mathbf{F_iO_2}$) or percentage (O_2%) of O_2 in the inspired gas
- The atmospheric pressure, i.e. the ambient gas pressure ($\mathbf{P_B}$), the water vapor pressure ($\mathbf{P_{H_2O}}$) *and* the respiratory quotient (**RQ –** normal value ≈ 0.8).
- The depth and frequency of ventilation, relative to the O_2 consumption of the body. This also determines the alveolar content of CO_2 gas, in normal lungs the alveolar and arterial CO_2 ($\mathbf{P_ACO_2}$ and $\mathbf{P_aCO_2}$) are close to equal.

$\mathbf{P_AO_2}$ can be calculated by the Alveolar Gas equation:

$$\mathbf{P_AO_2} = [(P_B - P_{H_2O}] \times F_iO_2 - P_aCO_2/RQ \approx \mathbf{P_aO_2}$$ (*222-225*).

Normal P_aO_2 at sea level is 13.3 kPa (100 mmHg). The quantity of O_2 at this pressure corresponds to 1-2% of the total O_2 content ($\mathbf{C_aO_2}$) of normal arterial blood. Breathing 100% O_2 (F_iO_2 1.0) may theoretically increase P_aO_2 6 to 7- fold (to 90 kPa (675 mmHg)) but increases the C_aO_2 by only around 10% (*68*).

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Effect of increasing the F_iO_2 on the P_aO_2.

In normal lungs with low tidal volumes and increased P_aCO_2.

Normal levels of P_aO_2 can be obtained by increasing the F_iO_2, provided the tidal volumes are well above the volume of the anatomical dead space (≈150 ml) (*220*). The P_aO_2 will be *close to* the calculated P_AO_2.

In dysfunctional lungs with normal or high tidal volumes.

Pulmonary diseases, trauma or inhalation of foreign material cause **pulmonary dysfunction**. The P_aO_2 is then always *lower* than the calculated P_AO_2, the difference increases with the severity of the lung dysfunction (*249*).

- If hypoxemia is due to increased numbers of alveoli with **reduced ventilation** but normal flow (*low* **V/Q ratios** (*233, 240*)), the P_aO_2 can usually be normalized by increasing the F_iO_2 but is lower than the calculated P_AO_2.
- If hypoxemia is caused by an increased number of alveoli with normal perfusion but **no ventilation** (fluid-filled or collapsed alveoli, alveoli distal to an airway occlusion, V/Q = 0, **pulmonary shunts,** *243-244*), the P_aO_2 increase in response to augmenting the F_iO_2 is modest. If shunting occurs in 33% or more of the alveoli, a F_iO_2 = 1.0. cannot normalize the PO_2 (*245*).

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Most diseased lungs contains a mixture of alveoli with *normal*, *reduced* or *no* ventilation. The effect on the P_aO_2 resulting from an increase of F_iO_2 reflects their relative ratio (*290*).

Additional interventions to increase the P_aO_2.

- Increasing the mean airway pressure during spontaneous breathing (Continuous Positive Airway Pressure, **CPAP** (*293-294*)) dilates the small airways, and may increase the total gas exchange area of the alveoli.
- If spontaneous tidal volumes are small, assisting or controlling the ventilation by mechanical devices have similar effects (*295-299*) and can in addition control the P_aCO_2 in most, but not all patients.
- If shunting is the predominant problem, increasing the O_2-content of the mixed venous blood ($\mathbf{C_vO_2}$) by increasing the $DO_2/\dot{V}O_2$ ratio (see below) will increase the P_aO_2 (*290*).
- In catastrophic lung failure, oxygenating the arterial blood by creating an artificial veno-arterial shunt, where the shunted blood passes through a gas exchange device (Extra Corporeal Membrane Oxygenation, **ECMO**), may increase the P_aO_2 (*316*).

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Targeting P_aO_2 levels in severe disease.

The P_aO_2 level does usually not represent a goal per se, its importance for the O_2 supply lies in the resulting S_aO_2 (see below). The F_iO_2 should, in most situations and patients, be titrated to obtain the P_aO_2 level that results in a satisfactory S_aO_2.

In **some acute** conditions (e.g. hyperacute circulatory failure, severe anemia, air embolization, and carbon monoxide intoxications) the P_aO_2 should be kept as high as possible by administration of F_iO_2 1.0 by whatever means in the initial phase (*181, 284-286*). A high P_aO_2 should then be a therapeutic goal *regardless* of measured S_pO_2 or S_aO_2.

Prolonged administration of F_iO_2 1.0 can be harmful (*44-45*). When the condition is stabilized or resolved, and adequate tissue oxygenation can be assumed, the F_iO_2 should be titrated to obtain a P_aO_2 level compatible with the desired S_aO_2 (see below). Reducing the F_iO_2 to 0.5 or lower should always be a goal after circulatory stabilization.

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S_aO_2, the arterial O_2 saturation of the Hb molecules *(2 slides)*

- Each Hb molecule can bind 4 O_2 molecules, the SO_2, i.e. the HbO_2 saturation, defines the number of Hb molecules that are saturated with O_2 molecules, as a percentage of all Hb. The quantity of Hb-bound O_2 is at all times in equilibrium with the PO_2 in the surrounding fluid; the relationship is non-linear and defined by the S-shaped HbO_2 curve, (*57*). The equilibrium shifts with changes in the Hb environment (*58*), variations in the Hb molecule structure, the valence of its Fe ion (*62-63*), and binding of carbon monoxide (CO) (*64-65*), see HbO_2 affinity below (*59-60*).
- In normal arterial blood, the HbO_2 saturation, $\mathbf{S_aO_2}$ is around 97.5%. The quantity of O_2 bound to the hemoglobin (HbO_2) then represents around 98.5% of the total number of O_2 molecules in the blood (*68*). While the P_aO_2, relative to F_iO_2, reflects the state of *gas exchange* in the lungs, the S_aO_2 is most important for the *O_2 content* of the blood.
- As tissue cells consume the O_2 dissolved in the interstitial fluid, more O_2 from plasma diffuse through the capillary wall. When the concentration of O_2 dissolved in plasma decreases (*47*), more O_2 is gradually released from Hb as the surrounding PO_2 decreases.

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- The quantity of O_2 bound to Hb (i.e. both the concentration of Hb *and* its O_2 saturation) is crucial for the capacity of the blood to maintain an adequate plasma PO_2 in the microcirculation and thus in the interstitial fluid.

Target values of S_aO_2 in severe disease.

- Regardless of P_aO_2, a S_aO_2 level of at least 94-96% should be the target in most acute situations with unstable circulation and/or severe anemia, while 90-92% may be a reasonable target in circulatory stable patients with normal Hb levels and function. In extreme acidosis and high body temperatures, supernormal P_aO_2 levels (20-30 kPa, or 150-225 mmHg) may be necessary to obtain normal S_aO_2 levels (*59-60*).
- In some patients, S_aO_2 values calculated by algorithms based on PO_2, pH and PCO_2 may be inaccurate. Such errors can occur especially in patients with *i)* very low PO_2, *ii)* CO intoxications, or *iii)* after multiple transfusions with stored blood. Modern blood gas analyzers often have built-in co-oximeters that measure the S_aO_2 directly. Clinicians should be aware of whether reported S_aO_2 levels represent *measured* or *calculated* values.

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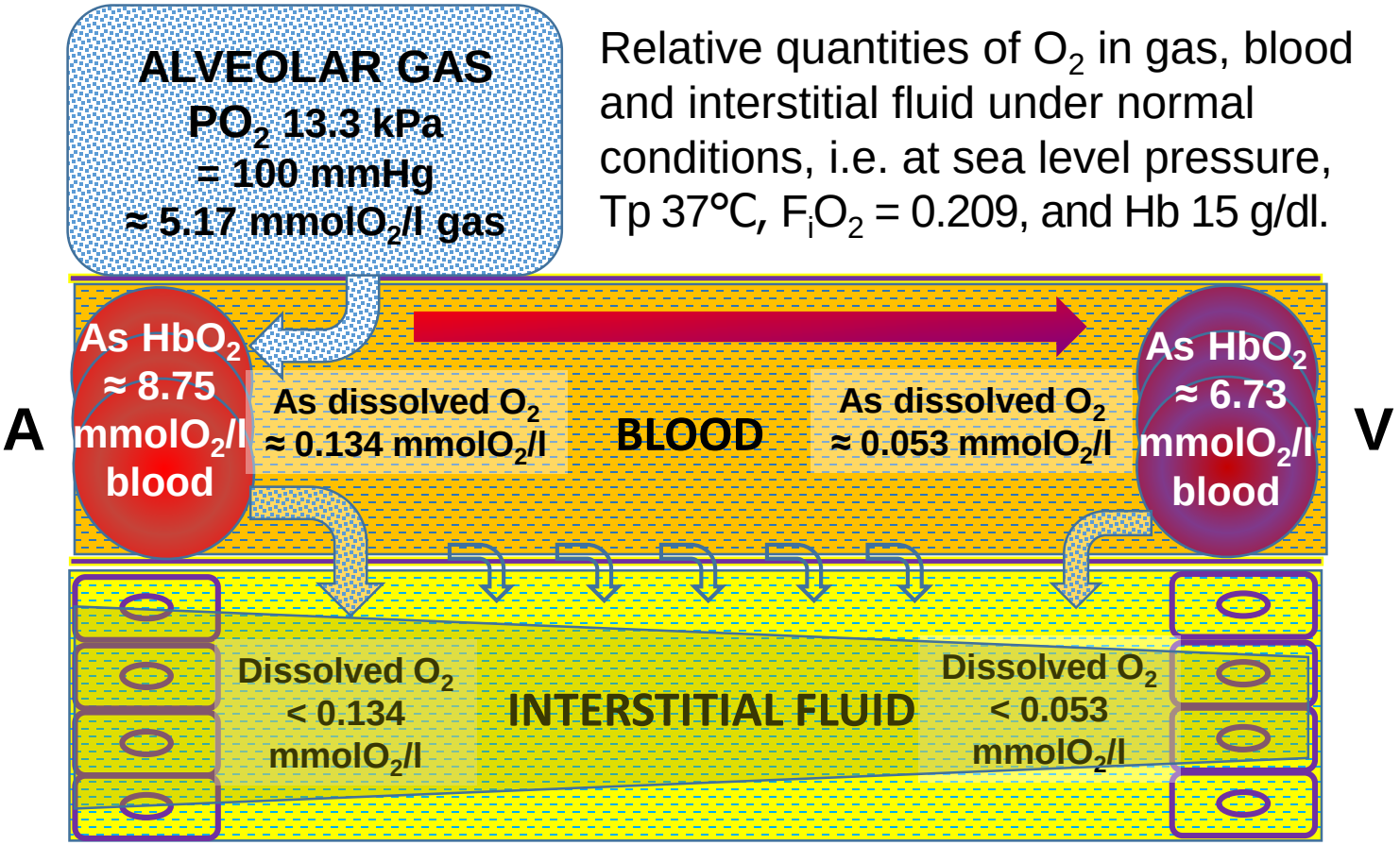

The figure displays the quantity of O_2 ***i)*** in the alveolar gas, ***ii)*** as bound to hemoglobin (HbO_2), and ***iii)*** as gas dissolved in plasma and interstitial fluid, see also (*69*). The unit mmol/l is a measure of the **quantity of O_2 molecules** bound to Hb *or* per volume of gas *or* dissolved in fluid (*416*).

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Hb affinity for O_2 changes with the Hb environment. *(2 slides).*

- At normal arterial HbO_2 affinity, a PO_2 of 13.3 kPa/100 mmHg corresponds to a SO_2 of 97.5%, a PO_2 of 8 kPa/60 mmHg to SO_2 of 91% and a PO_2 of 5.3 kPa/40 mmHg to SO_2 of 75% (*57*). The equilibrium between the HbO_2 (as SO_2) and PO_2 is affected by endogenous factors like pH, Tp, 2-3 DPG, and PCO_2 of the blood (*59-60*), and others (e.g. carbon monoxide (CO), nitrous agents, etc. *64-66*). It may also change due to genetic variations in the Hb molecule (*62-64*)**.** Blood stored for more than 2 weeks have an increased HbO_2 affinity due to a reversible loss of 2-3 DPG from the erythrocytes (*62*).
- In clinical medicine, affinity changes induced by changes in blood pH (*59*) and temperature (*60*) are the most important. Changes in blood PCO_2 exert their effect mostly through the simultaneous effects on pH. When pH changes from 7.40 to 6.80, the S_aO_2 corresponding to a P_aO_2 of 8 kPa (60 mmHg) is reduced from 91% to about 60% (*59*). At lower PO_2 values, the reduction is even more pronounced. On the other hand, in alkalotic blood (pH 7.70) or blood with a high percentage of fetal Hb, the SO_2 corresponding to very low PO_2 values increase substantially (e.g. at a PO_2 of 4 kPa (30 mmHg), SO_2 increases from about 55% at normal pH to 75-80%).

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- Normal affinity of Hb molecules for O_2 requires an intraerythrocyte environment. Only Hb molecules *inside* the erythrocytes are effective O_2-transporters. Outside the erythrocytes, the HbO_2 affinity changes so much (due to lack of 2-3 DPG) that almost no O_2 is released from the Hb molecules before plasma and interstitial PO_2 falls below the critical threshold. Hb molecules dissolved in plasma after hemolysis are thus ineffective as O_2 carriers in the human organism (*60*).

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Hb concentration in the blood. *(2 slides)*

- The Hb concentration depends on the balance between erythrocyte production and their Hb content on one side, and Hb loss due to hemolysis, hemorrhage, or therapeutic phlebotomy on the other. While normal Hb concentration in the blood is in the 12-16 g/dl range, healthy volunteers with normal circulatory capacity can tolerate acute reductions to around 5 g/dl as long as normal blood volume is maintained (*130*). Levels of 2 g/dl or even lower may be compatible with survival (*83-84*).
- In most persons, the Hb concentration is proportional to the erythrocyte concentration. The latter is an important determinant of the blood viscosity (*120, 419-420*), which affect both the microcirculatory flow and the resistance to ejection of blood from the ventricles. The effect of increasing the Hb may vary between healthy persons and different groups of patients; it increases the O_2 content of the blood and the work capacity in athletes, on the other hand, it reduces C.O. and microcirculatory blood flow (see DO_2 below) in persons with reduced cardiac capacity.

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Target values of Hb concentration in severe disease.

Hb 10 g/dl has been found to be adequate in connection with surgery and 7.0 g/dl have been recommended as a lower limit for severely ill patients (*83-84*). The target value for Hb in most stabilized patients should be in the 7-10 g/dl range. An adequate cardiac reserve, i.e. the capacity for increasing the cardiac output when the O_2 content of the blood is reduced, is a pre-requisite for tolerance to low Hb levels (*71-72*).

Focusing on Hb levels *alone* is too simplistic as the Hb concentration is only one of the three factors that govern the amount of O_2 delivered to the tissues (**DO_2**, see below). Whether or not to transfuse blood to patients with low Hb should include an assessment of

- The oxygen status (P_aO_2 and S_aO_2) of the arterial blood,
- The assumed (or measured) capacity for increasing cardiac output, *and*
- The assumed (or measured) changes in metabolic rate (i.e. the O_2 consumption).

The last two factors will affect the SO_2 difference between arterial and mixed venous blood (high precision) or central venous blood (lower precision) (*175 -177)*.

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Arterial blood O_2 content, C_aO_2.

(2 slides)

The **C_aO_2** is a function of Hb, S_aO_2 and P_aO_2 levels. Under normal conditions, the O_2 content of the blood of most patients may be considered to be proportional to the concentration of Hb and its saturation, while the importance of P_aO_2 is mostly limited to its impact on the SO_2 (66-68).

The O_2-binding capacity of normal Hb, when 100% saturated, is usually given as 1.34 mlO_2/gHb, and the quantity of O_2 dissolved at 37°C is 0.225 mlO_2/kPa/l. The C_aO_2 value for normal arterial blood is close to 200 mlO_2/l blood, and is calculated as

$$\mathbf{C_aO_2} = [(1.34\ mlO_2/gHb \times \mathbf{Hb}\ g/l \times \mathbf{SO_2}/100)) + (0.225\ mlO_2/l/kPa \times \mathbf{P_aO_2})]$$

or as a bedside simplification: C_aO_2 (mlO_2/l) ≈ (Hb + ⅓Hb) g/dl x S_aO_2/10. (*68*)

In catastrophic anemia, or when the Hb molecules cannot transport O_2 (e.g. carbon monoxide intoxication), the importance of dissolved O_2 for the C_aO_2 increases. At a P_aO_2 of 250 kPa (1875 mmHg), the quantity of dissolved O_2 is sufficient to cover the O_2 consumption at rest with a normal C.O (*67*).

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To achieve such a P_aO_2, a person with perfect lung function must breathe gas with a F_iO_2 of 1.0 at an ambient pressure of about 2.5 atmospheres, i.e. during dives below 15 meters depth *or* in high-pressure chambers. Such P_aO_2 levels are toxic (*44-45*), and should be utilized only for limited periods.

Target values of C_aO_2 in severe disease.

The target value for individual patients should depend on their capacity for increasing the C.O. A C_aO_2 reduction to about 40% of normal is well tolerated in healthy individuals (*129-130*) but may be poorly tolerated in patients with circulatory co-morbidities.

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Cardiac output, C.O., the total blood flow to the organism *(2 slides)*

- The normal C.O. of a 70-75 kg person with normal body configuration at rest is 5-6 l/min. It increases by 50-100% during modest muscular activity and by 400% or more in well-trained athletes during strenuous exercise (*129*). In a healthy organism, the C.O. also adapts rapidly to changes in C_aO_2 as well as O_2 consumption of the organism. Cardiac output is a crucial factor for tissue oxygenation; substantial reductions in C_aO_2 can be compensated for by increased C.O. while the opposite strategy has a very limited application. The organism is sensitive to reductions in C.O., a reduction by 30% from normal at normal body temperature leads to tissue hypoxia and is defined as cardiogenic shock (*135, 159*).
- In order to increase the C.O., the venous return and the compliance of the ventricles (i.e. the filling volumes of the ventricles) must be adequate. In addition, all conditions that have a negative effect on the systolic and diastolic function of the chambers, as well as on valvular function, impedes the normal cardiac adaption to a reduced C_aO_2 (*133-148*). Reductions in C_aO_2 that are well tolerated by young, healthy volunteers may result in tissue hypoxia in persons with a reduced cardiac reserve capacity (*82-84*).

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Target values of C.O. in severe disease.

- The ability to tolerate reductions in PO_2, S_aO_2 and Hb levels rests on the capacity for increasing the C.O. Whether the target C.O. value should be above normal when the C_aO_2 is reduced, and by how much, depends on the relationship between C_aO_2 and C.O. on one side, and the O_2 consumption of the whole organism or sensitive tissues on the other. For individual organs, the perfusion pressure and local vascular conditions are more important than the C.O. *per se*, on the other hand, a low C.O. is associated with reduced perfusion pressure in most patients.
- A reduced ABP does not necessarily imply a low C.O. Both stroke volumes and C.O. may be increased *above* normal if the reduced ABP is due to systemic vasodilatation with a preserved or increased preload (*127*).
- All interventions aiming at increasing the C.O. in severely ill patients may have negative effects (e.g. reduced lung function and P_aO_2/S_aO_2 with increasing the blood volume by fluid infusions, increased risk of myocardial hypoxia and arrhythmias during inotropic myocardial stimulation). The need for such interventions should be carefully evaluated.

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O_2 delivery to the organism (all tissues). *(2 slides)*

The DO_2 changes proportionally with the O_2 content of the blood and the cardiac output

DO_2 mlO_2/min **= C_aO_2** mlO_2/l **x C.O.** l/min

With a normal C.O. of 5 l/min and a C_aO_2 of 200 mlO_2/l blood, the volume of O_2 supplied to a resting organism per minute (**DO_2**) is ≈ 1 000 mlO_2/min (or ≈ 44.6 $mmolO_2$/min, *416-418*). This is about 4 times that of the normal resting O_2 consumption, $\dot{V}O_2$, of the whole organism (*69*). The *effective* DO_2 is slightly smaller, as the last 7-8% of the O_2 in the blood cannot be utilized by the tissues before hypoxia commences (*57-58*). The ratio between O_2 supply and consumption differs greatly between various organs (*42*); the beating heart consumes 50-60% or more of the supplied O_2.

Of the three factors that determine the DO_2, low Hb is best tolerated. A reduction to 33-25% of normal can easily be compensated for by increases in C.O. in otherwise healthy persons; such an increase is facilitated by the reduced viscosity of blood with a reduced erythrocyte content (*420*).

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- A chronic reduction of S_aO_2 (e.g. prolonged stay at high altitudes, chronic lung diseases) to around 90 % of normal is usually accompanied by increased Hb levels. Such persons can therefore have a normal or raised C_aO_2, but the increased viscosity reduces their capacity for augmenting the C.O.
- The tolerance to acute S_aO_2 reductions is more limited. An acute S_aO_2 reduction to 80% or below can be critical, a S_aO_2 of 70% is, according to the authors experience, the lowest value where young patients with an adequate cardiac reserve may survive for days without detectable organ damage. Even if well-trained mountaineers with increased Hb values can tolerate a S_aO_2 down to around 55% (*239*), an acute reduction in S_aO_2 to similar levels in patents is life-threatening (*235*).
- Acute reductions in C.O. is poorly tolerated. A reduction to 70% of normal is defined as cardiogenic shock, i.e. a state of insufficient tissue oxygenation due to reduced tissue perfusion. The effect of increase in C_aO_2 by increasing F_iO_2 is modest unless there is a concomitant hypoxemia. The effect of increasing the C_aO_2 by increasing the Hb acutely by blood transfusions also increase blood viscosity, which may reduce both C.O. and microcirculatory flow.

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Local perfusion flow.

- An adequate DO_2 to the organism as a whole is a prerequisite for adequate tissue oxygenation within the various organs. The perfusion flow (Q) of individual organs, however, is determined by the perfusion pressure (P) (mainly the arterial minus venous blood pressure) modified by the vascular resistance of the local vessels (R):

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

- To maintain a stable perfusion, increased resistance must be compensated for by increased perfusion pressure. On the other hand, decreased resistance with unchanged perfusion pressure results in increased tissue flow.

Tissue O_2 supply.

- The O_2 supply to an organ becomes a function of the perfusion flow *and* the O_2 content of the perfusing blood. Whether the supply is sufficient for maintaining normal organ function depends on the metabolic activity of the tissues, which determine the O_2 consumption, the $\dot{V}O_2$ (next slide).

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Tissue O_2 consumption, $\dot{V}O_2$.

At rest (i.e. no use of muscles other than the respiratory ones), the normal O_2 consumption of the organism is around 250 ml O_2/min in a 70 kg person with normal build. The three most common examples of increased $\dot{V}O_2$ are

- Muscular exertion (including epileptic fits and shivering) where the $\dot{V}O_2$ may increase 10-fold or more,
- Increases in body temperature (fever) and
- A rise in metabolic rate due to hormonal effects (e.g. thyroid hormones, catecholamines).

The latter effects may increase the $\dot{V}O_2$ by 20-100% (*42*). A *reduction* in $\dot{V}O_2$ (i.e. a reduced metabolic rate), is induced by hypothermia (*43*), deep sedation, *or* mitochondrial dysfunction (rare) also reduce the $\dot{V}O_2$.

The total $\dot{V}O_2$ of the organism can be measured directly by comparing the O_2 content of inspiratory and expiratory gas, *or* calculated from measurements of the O_2 content in arterial and mixed venous blood *and* the C.O. (*9*).

The local tissue O_2 consumption within an organ can be measured in laboratories, but cannot be measured by methods commonly available at the bedside.

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The $DO_2/\dot{V}O_2$ ratio.

(3 slides)

- The $DO_2/\dot{V}O_2$ ratio is a measure of the relationship between the O_2 supply and consumption to the organism. The ratio in a normal resting organism is around 4:1 (DO_2 of 1000 mlO_2/min *vs* $\dot{V}O_2$ of 250 mlO_2/min), the ratios for individual organs varies substantially (*41-42*). A ratio of 2:1 (i.e. DO_2 500 mlO_2/min) for the whole organism should be considered critical (*80-82*).
- The normal organism rapidly adapts the DO_2 to changes in $\dot{V}O_2$. In the lungs, the adaption consists of changing the ventilation depth and/or frequency; hyperventilation with a reduction of P_ACO_2 may increase the PO_2 in the alveolar gas (*223*) and thus the S_aO_2. The cardiac output also changes in response to changes in C_aO_2 and $\dot{V}O_2$; the C.O. increase during exercise in healthy persons is about 50% of the $\dot{V}O_2$ increase (*43, 129*)**.**
- Comparison of the arterial and mixed venous SO_2 (**S_VO_2,** normal value 72-75%), when corrected for the actual Hb, provides a rough indicator of the relationship between O_2 supply and consumption in the whole organism (*72*). For *quantitative* analysis, the O_2 content of arterial and mixed venous blood must be calculated, i.e. the Hb and PO_2 levels must be included in the calculation.

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- A reduced $DO_2/\dot{V}O_2$ ratio leads to increased extraction of O_2 from the blood, reflected by a reduced SO_2 in central (least accurate) - and mixed venous (most accurate) blood (*72, 81*). During severe reduction of the $DO_2/\dot{V}O_2$ ratio, the tissue PO_2 at some point becomes so low that aerobic metabolism can no longer be maintained by all tissue cells (*81, 82*).
- Changes in blood lactate is often used to indicate whether the lower limit for DO_2 has been reached; the combination of low mixed- or central venous SO_2 *and* increased lactate levels in the blood *at rest* is a strong indicator of insufficient DO_2. In patients with mitochondrial dysfunction, increased lactate production may be accompanied by a *reduced* $\dot{V}O_2$ and a high venous SO_2. Increased lactate levels are not always associated with reduced DO_2 (*89-90*).
- In critical conditions, reduction of $\dot{V}O_2$ by deep sedation and mild hypothermia may be an adjunct strategy if efforts to increase the DO_2 fail to secure a satisfactory $DO_2/\dot{V}O_2$ ratio. A bonus effect of reducing the $\dot{V}O_2$ is an increase in C_aO_2 if pulmonary shunting reduces the P_aO_2 and S_aO_2 (*290*).

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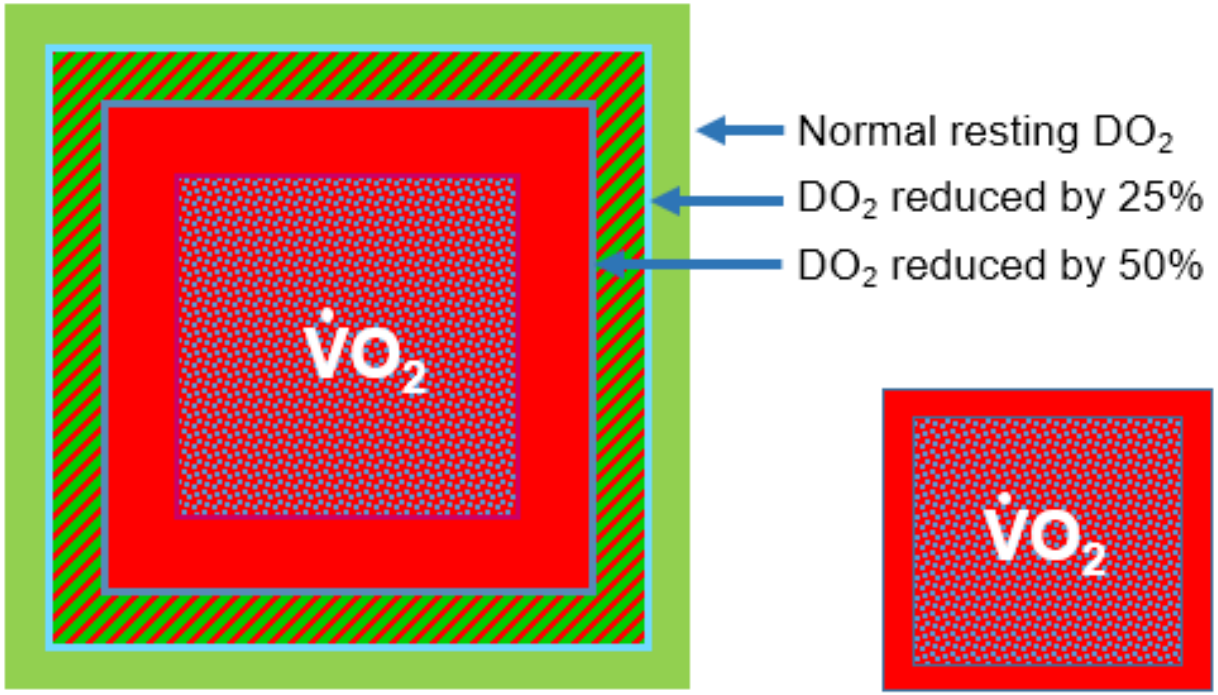

Graphic presentation of the relationship between the DO_2 and $\dot{V}O_2$ for the whole organism and the heart, drawn to different scales. If heart failure is the cause of a reduced DO_2 a 25% reduction can become critical. Persons with severe anemia as the only problem can tolerate a 50% reduction without signs of tissue hypoxia. The heart consumes 50-60% of its O_2 supply, and depends on increased perfusion when the O_2 consumption increases.

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Tissue ischemia.

Ischemia denotes a condition where insufficient tissue O_2 supply is due to vascular *obstruction* (partial ischemia causing tissue hypoxia) or total *occlusion* of blood flow (rapidly resulting in tissue anoxia). The supply of nutrients is also reduced or lacking, which limits the capacity of the cells to utilize anaerobic metabolism as an alternative source of energy (*79*).

Tissue anoxia.

In anoxia, no O_2 reaches the tissues. It is most common in association with no-flow conditions (vascular occlusion or cardiac arrest).

Tissue hypoxia.

Even if hypoxia strictly means only that the amount of O_2 reaching tissues is in the subnormal range, the term is usually used for conditions where the O_2 supply is *insufficient* to sustain normal function of all tissue cells. It is important to discriminate between hypoxia and hypoxemia, as the latter is compatible with normal tissue oxygenation if the circulatory compensation is adequate. Subnormal PO_2 levels may induce functional changes in cells (signaling effects) without inducing acute dysfunction.

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Various tissues have different tolerance to anoxia and hypoxia, with cells of the cerebral cortex and the myocardium having the lowest tolerance (*86, 161*).

Tissue normoxia.

Normoxia, in the meaning that adequate tissue oxygenation is sustained, may be maintained during hypoxemia if the latter is compensated by a close to proportional increase in tissue blood flow (*71-72*).

Mitochondrial dysfunction.

Mitochondrial dysfunction (due to e.g. post hypoxic damage, toxins, and inborn defects) may inhibit aerobic metabolism despite normoxia or hyperoxia (*75, 82, 89-90*). The degree of dysfunction decides whether the affection of the mitochondria results in tissue dysfunction, damage or death. Post hypoxic mitochondrial damage may occur after a period of hypoxia/ anoxia. During the period after reperfusion/ reoxygenation have been established, high P_aO_2 levels may have detrimental effects (*86-87*).

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Duration of O_2 deprivation.

The duration of episodes of ischemia, anoxia or hypoxia, is a critical factor for the consequences of such episodes. In the most O_2-sensitive cells, dysfunction may be induced by only 5-20 sec of anoxia. A few minutes of anoxia may be sufficient to cause irreversible damage to the most sensitive brain cells; myocardial cells may survive a period of 15-20 minutes or more (*86*) while skeletal muscle may tolerate 1-2 hours.

Consequences of Hypoxia/Anoxia.

Signaling effects are changes in cell function that occur when the surrounding PO_2 becomes low, without obvious dysfunction of the normal cell functions. Examples of this are the local vasocontraction in the lungs induced by reduced alveolar PO_2 (HPV, *230)* and the generation of hypoxia-inducible factor (HIF) by cardiomyocytes in response to episodes of low tissue PO_2.

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Cell dysfunction may be a *temporary* decrease or loss of normal cell function. If the cause is temporary hypoxia, and adequate oxygenation is rapidly re-established, cells regain normal function within seconds to minutes. A common example is a vaso-vagal syncope, where consciousness may return within seconds after normalization of cerebral perfusion pressure, followed by normal cerebral function within few minutes.

Cell damage occurs if the severity and duration of hypoxia/anoxia cause prolonged dysfunction of the cells, but when their function may be regained if adequate oxygenation is restored before damage becomes irreversible (e.g. myocardial stunning (*137*)).

Cell death occurs if the severity and duration of hypoxia/anoxia cause the damage to become irreversible.

Tissue damage of clinical importance results when a substantial number of tissue cells die. As the O_2 supply may be unevenly distributed within an organ, some cells may regain normal function after adequate O_2 supply has been re-established. The quantity of irreversibly damaged cells *vs* those that survive determine whether clinical organ failure ensues or not.

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