Classes of tissue hypoxia

OLE SIGGAARD-ANDERSEN, ANNETTE ULRICH & IVAR H. GOTHGEN

Department of Clinical Biochemistry, Herlev Hospital, Department of Surgery, Roskilde Hospital, Department of Anaesthesia, Gentofte Hospital, DK

We identify eight causes of tissue hypoxia, falling into three classes, A, B, and C, depending upon the effect on the critical mixed venous $pO_2$ and the optimal oxygen consumption rate. The critical mixed venous $pO_2$ is the value above which the oxygen consumption rate is optimal and independent of the mixed venous $pO_2$ and below which the oxygen consumption rate decreases towards zero. Class A hypoxia: primary decrease in mixed venous $pO_2$. Causes: 1) ischemic hypoxia (decrease in cardiac output), 2) low-extractivity hypoxia (decrease in oxygen extraction tension, $p_x$).

Class B hypoxia: primary increase in critical mixed venous $pO_2$. Causes: 1) shunt hypoxia (increased a-v shunting), 2) dysperfusion hypoxia (increased diffusion length from erythrocytes to mitochondria and/or decreased total capillary endothelial diffusion area, e.g. tissue oedema, microembolism), 3) histotoxic hypoxia (inhibition of the cytochrome chain). Class C hypoxia: primary increase in optimal oxygen consumption rate. Causes: 1) uncoupling hypoxia (uncoupling of the ATP formation associated with $O_2$ reduction), 2) hypermetabolic hypoxia (increased energy metabolism, e.g. due to hyperthermia).

Key words: arterial blood; blood flow; energy metabolism; mixed venous blood; oxygen, - consumption rate, - delivery, - tension;

Several clinical studies have shown that survivors from critical illness and intensive care tend to have higher oxygen delivery and oxygen consumption rate than non-survivors (1, 2). This has led to the concept of a critical oxygen delivery (3). During critical illness (trauma, adult respiratory distress syndrome, sepsis) the critical oxygen delivery and the optimal oxygen consumption rate both tend to be higher than normal (Fig. 1).

Fig. 1. Oxygen consumption rate as function of oxygen delivery, both relative to body surface area. Below the critical oxygen delivery the oxygen consumption rate becomes delivery dependent and decreases linearly. A is the normal critical point. B exemplifies a state of critical illness with increased critical oxygen delivery and increased optimal oxygen consumption rate. The ellipse is the normal reference area.

We have previously shown that the critical oxygen delivery depends on the cause of low delivery (4). For example, if oxygen delivery is halved due to a 50 % reduction in cardiac output, then the mixed venous oxygen tension decreases to about 3.5 kPa. However, if the reduction in delivery is due to a low arterial total oxygen concentration caused by a low arterial oxygen tension, then the mixed venous oxygen tension is as low as 2.2 kPa. The mixed venous oxygen tension is closely related to the average end capillary oxygen tension which determines the diffusion gradient for oxygen from erythrocytes to mitochondria. It is therefore more relevant to postulate the existence of a critical mixed venous oxygen tension than a critical oxygen delivery.

The purpose of the present study was to analyze the relationship between the mixed venous oxygen tension and the oxygen consumption rate in connection with different types of hypoxia. The result is a classification of tissue hypoxia in three well defined classes. All calculations were performed with the Oxygen Status Algorithm, a common resource computer program (5).

SCHEMATIC MODEL

Oxidative metabolism in man is based upon: 1) convective oxygen transport from ambient air to blood capillaries, with haemoglobin and erythrocytes as vehicles, 2) oxygen diffusion from erythrocytes in the capillaries to mitochondria in the cells, and 3) oxygen reduction in the mitochondria with "transport" of the electrons from the reductants (carbohydrate, fat, or protein) to oxygen via the electron transport chain, composed of cytochromes, flavin coenzymes, and niacin nucleotides (Fig. 2).
Fig. 2. Schematic model of oxygen transport and reduction. The numbers are representative for a normal 70 kg adult. For explanation see text and alphabetical list of symbols.
Oxygen convection:

The substance rate of oxygen convection in the blood stream, the "oxygen delivery" ($nO_2$flow), is the product of cardiac output ($V_B$flow) and concentration of total oxygen in the arterial blood ($c_{tO_2a}$): $nO_2flow = V_Bflow \cdot c_{tO_2a}$. The rate of oxygen extraction from the blood ($nO_2$extr) is the product of cardiac output and arterio-venous total oxygen concentration difference ($Dc_{tO_2av}$): $nO_2extr = V_Bflow \cdot Dc_{tO_2av}$.

Oxygen diffusion:

The substance rate of oxygen diffusion from haemoglobin to cytochrome aa₃ ($nO_2$diff), may be derived as the product of the diffusion coefficient ($D_{O_2}$), the solubility coefficient ($α_{O_2}$), the total capillary endothelial diffusion area ($A$), and the oxygen tension gradient ($dpO_2/dl$): $nO_2diff = D_{O_2} \cdot α_{O_2} \cdot A \cdot dpO_2/dl$. The product of diffusion coefficient and solubility coefficient is the permeability coefficient ($κ_{O_2}$). The ratio between the diffusion area and distance increases in working muscles by capillary recruitment. The ratio decreases with tissue oedema or micro embolism. The oxygen tension gradient is the mean oxygen tension difference ($pO_2$cap - $pO_2$cell) divided by the mean distance between erythrocytes and mitochondria. The limiting factor for oxygen diffusion tend to be the end capillary oxygen tension. The mixed venous oxygen tension almost equals the latter although arterio-venous shunting must be taken into account. If arterio-venous shunting in the skin or elsewhere increases to say 10 % of the total cardiac output then the mixed venous oxygen tension will be about 0.3 kPa higher than the mean end capillary oxygen tension. Flow redistribution, such as increased skin perfusion, represents increased functional arterio-venous shunting.

Oxygen reduction:

Oxygen reduction in the mitochondria is normally a zero order reaction which depends on energy requirements rather than available oxygen. Hyperbaric oxygen, for example, does not increase oxygen consumption. In other words, the rate of oxygen diffusion ($nO_2$diff) and extraction ($nO_2$extr) adjust themselves to match the rate of oxygen reduction, $nO_2$red. The latter is regulated somehow by the ATP/ADP ratio. 90 % of oxygen reduction occurs in the mitochondria, where reduction of one oxygen molecule is coupled to phosphorylation of six molecules of ADP to ATP. In some tissues, like the brown fat in some mammals, oxygen reduction is associated with the production of heat only without formation of ATP. Some toxic agents and drugs uncouple ATP formation from oxygen reduction. The energy produced by reduction of oxygen is about 450 kJ/mol, somewhat dependent upon the kind of fuel (carbohydrate, fat, or protein). Useful chemical energy associated with hydrolysis of ATP is about 50 kJ/mol.

Oxygen reduction becomes a first order reaction with a rate proportional to the cell cytosol $pO_2$ when the latter decreases below a critically value of about 0.1 kPa (Fig. 3). The normal average cell $pO_2$ is about 1.6 kPa, with a considerable variation among different tissues. Toxic inhibition of the cytochromes responsible for the catalytic reduction of oxygen increases the critical cell $pO_2$. Cyanide poisoning, for example, may completely block catalytic oxygen reduction.

![Fig. 3. Oxygen reduction rate as function of cell $pO_2$. Oxygen reduction is a zero order reaction when cell $pO_2$ is above a critical value of about 0.1 kPa. Below that value, oxygen reduction becomes a first order reaction with a rate proportional to the cell $pO_2$. The normal average cell $pO_2$ is about 1.6 kPa, well above the critical level.](image)

The normal average end capillary $pO_2$ is about 5.0 kPa, with a considerable variation among different tissues. The average $pO_2$ difference between erythrocytes and mitochondria is about 3.4 kPa (Fig. 4). Oxygen breathing increases the end capillary and the cell $pO_2$ to the same extent so that the $pO_2$ difference and the rate of oxygen diffusion remains constant, the latter matching the oxygen reduction rate. If the end capillary $pO_2$ decreases, for example due to a decrease in arterial $pO_2$, the cell $pO_2$ decreases equally much and the diffusion gradient and the diffusive flux remains unaffected until the critical point is reached where the end capillary $pO_2$ has decreased to 3.5 kPa and the cell $pO_2$ to 0.1 kPa. A further decrease in end capillary $pO_2$ causes a decrease in oxygen reduction rate. If, for example, the end capillary $pO_2$ decreases to 1.7 kPa, then the cell $pO_2$ decreases to 0.05 kPa; the rate of oxygen diffusion is halved and now determines the rate of oxygen reduction which is likewise halved.
**OXYGEN REDUCTION RATE & MIXED VENOUS $pO_2$**

The relationship between oxygen reduction rate and mixed venous $pO_2$ is shown in Fig. 5.

**Primary change in mixed venous $pO_2$:**

If the mixed venous $pO_2$ increases, for example due to oxygen inhalation, the oxygen consumption rate remains constant and the point $v$ in Fig. 5 moves horizontally to the right. If the increase in mixed venous $pO_2$ is due to an increase in cardiac output the oxygen consumption rate would increase due to the increased cardiac work and the horizontal line would tilt slightly upwards.

If the mixed venous $pO_2$ decreases, point $v$ moves (almost) horizontally to the left until the critical point $A$ is reached. A further reduction in mixed venous $pO_2$ causes a decrease in oxygen consumption rate. The breaking point at $A$ is actually a bend, due to the heterogeneity of the critical mixed venous $pO_2$ among different tissues.

With a normal oxygen status and oxygen consumption rate, doubling the cardiac output increases the mixed venous $pO_2$ from 5.0 to about 6.6 kPa. Halving the cardiac output reduces the mixed venous $pO_2$ to about 3.5 kPa. A change in the arterial oxygen extraction tension causes an almost identical change in the mixed venous $pO_2$, and if the arterio-venous oxygen concentration difference happens to be 2.3 mmol/L, the mixed venous $pO_2$ practically equals the arterial oxygen extraction tension.

**Changing the average oxygen diffusion area/distance ratio:**

The position of the critical point $A$ and the oblique line of "$pO_2$ dependent oxygen consumption" depends on the oxygen diffusion area/distance ratio. An increased ratio caused by capillary recruitment causes a shift of the oblique line to the left with a decrease in critical mixed venous $pO_2$. A decreased ratio shifts the line to the right and increases the critical mixed venous $pO_2$. An increased arterio-venous shunting also shift the line to the right.

**Primary change in oxygen consumption rate:**

If the oxygen consumption rate increases at constant cardiac output and temperature, then the arterio-venous oxygen concentration difference increases and the mixed venous $pO_2$ decreases. The point $v$ moves upwards to the left. A reduction in oxygen consumption rate causes the opposite changes. The slope of the relationship, i.e. slope of constant cardiac output, is about $-2$ in Fig. 5.

**Varying temperature:**

The optimal oxygen consumption rate changes with temperature with about 9 %/°C. Cardiac output is likely to change equally much so that the arterio-venous oxygen concentration difference remains constant. Hence the change in mixed venous $pO_2$ with temperature equals the change in the position of the oxygen dissociation curve, i.e. the change in the halfsaturation tension with temperature.

During hypothermia the mixed venous $pO_2$ is lower when pH and $pCO_2$ are regulated according to the α-stat approach ($pH$ and $pCO_2$ varying with temperature as in a blood sample in vitro) than with the pH-stat approach ($pH$ and $pCO_2$ constant). At 27 °C the mixed venous $pO_2$ has dropped from 5.0 kPa to 3.0 kPa with the pH-stat and to 2.5 kPa with the α-stat. The intersection point between the horizontal line for 27 °C and the oblique line (Fig. 5) indicates a critical mixed venous $pO_2$ of 1.5 kPa. However, the permeability coefficient for oxygen decreases about 1 %/°C. Therefore the critical mixed venous $pO_2$ must be somewhat higher, probably about 1.7 kPa. Nevertheless, the mixed venous $pO_2$ remains well above the critical value even with the α-stat approach.
CLASSES OF TISSUE HYPOXIA

Fig. 5. Relationship between mixed venous $pO_2$ and oxygen reduction rate related to body surface area in a double logarithmic plot. The circle indicates normal values for a 70 year old man. The heavy line shows the relationship when the mixed venous $pO_2$ is the independent variable. A is the critical point. The position of the oblique line of slope 1 depends on the ratio of diffusion area and average diffusion distance ($A/l$). The dashed lines of slope -2 show the relationship when the oxygen consumption rate is the independent variable and cardiac output remains constant. The position of the horizontal line depends on energy requirements and body temperature. The oblique lines labelled $\alpha$-stat and pH-stat indicate the relationship between oxygen consumption and mixed venous $pO_2$ with varying temperature at constant arterio-venous oxygen concentration difference.

CAUSES OF TISSUE HYPOXIA

We have previously identified eight causes of tissue hypoxia, meaning a state where oxidative energy production is insufficient and glycolytic energy production takes over with ensuing lactic acidosis and cellular malfunction (4):

1. Low cardiac output ($\dot{V}B$) causes ischemic hypoxia.
2. Low oxygen extraction tension ($p_x$) causes low extractivity hypoxia. The causes of a low $p_x$ are low arterial $pO_2$ (hypoxemic hypoxia), low effective haemoglobin concentration (anaemic hypoxia), or low halfsaturation tension (high affinity hypoxia). The arterial oxygen extraction tension is defined as the oxygen tension obtained after extraction of a standard amount of oxygen (2.3 mmol) per litre blood. The oxygen extraction tension indicates the degree of compensation among the arterial $pO_2$, the effective haemoglobin concentration, and the halfsaturation tension (4). The oxygen extraction tension is calculated on the basis of standard pH-blood gas measurements by an algorithm similar to the calculation of the halfsaturation tension (5).
3. Increased arterio-venous shunting ($F_{av}$) causes shunt hypoxia.
4. Increased mean diffusion distance for oxygen (\(d_{\text{diffus}}\)) causes dyserfusion hypoxia.
5. Decreased endothelial diffusion area for oxygen (\(A_{\text{diffus}}\)) also causes dyserfusion hypoxia.
6. Inhibition of the cytochromes by toxic agents (cyt. inhib.) causes histotoxic hypoxia.
7. Decreased ratio between ATP formation and oxygen reduction causes uncoupling hypoxia.
8. Increased energy metabolism causes hypermetabolic hypoxia.

Quantitative measures of these causes of hypoxia are only available for the first two: cardiac output and arterial oxygen extraction tension. The other causes of tissue hypoxia must be evaluated clinically. Overhydration and tissue oedema gives a suspicion of decreased diffusion area and increased diffusion length. Hyperthermia and sepsis gives a suspicion of hypermetabolic hypoxia.

Table 1. Causes and effects of tissue hypoxia, leading to the classification of causes on the basis of effects.

<table>
<thead>
<tr>
<th>Hypoxia class</th>
<th>Optimal oxygen consumption rate</th>
<th>Critical mixed venous (pO_2)</th>
<th>Actual mixed venous (pO_2)</th>
<th>Hypoxia type</th>
<th>Primary disturbance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>normal</td>
<td>normal</td>
<td>decrease</td>
<td>ischemic h.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>low FB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>low (p_x)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>low (pO_2a)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>low ceHb</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>low (p_30)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>normal</td>
<td>increase</td>
<td>increase</td>
<td>shunt h.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dyserfusion h.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>histotoxic h.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>high (F_{av})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>high (d_{diffus}), low (A_{diffus})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cytochrome inhibition</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>increase</td>
<td>increase</td>
<td>decrease</td>
<td>ATP-uncoupling h.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>hypermetabolic h.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>low n(ATP_{ox}/nO_2_{red})</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>high (rO_2_{red})</td>
<td></td>
</tr>
</tbody>
</table>

CLASSES OF TISSUE HYPOXIA

On the basis of the effects on the mixed venous \(pO_2\) and the oxygen consumption rate, the eight causes of tissue hypoxia fall into three classes (Fig. 6 and Table 1).

Class A hypoxia.
The primary disturbance is a decrease in mixed venous \(pO_2\) with no change in optimal oxygen consumption rate. When \(pO_2v\) decreases below the normal critical point \(A\), the oxygen consumption rate decreases (exemplified by point \(a\)), resulting in glycolysis and lactic acidosis. The causes of Class A hypoxia are low cardiac output and/or low oxygen extraction tension. A low value of either may be compensated by an increased value of the other. The therapeutic goal is to raise the mixed venous \(pO_2\) above the critical level (point \(A\)) to ensure an optimal oxygen consumption rate.

Class B hypoxia.
The primary disturbance is an increase in critical mixed venous \(pO_2\) with no change in optimal oxygen consumption rate. When the critical mixed venous \(pO_2\) increases above the normal mixed venous \(pO_2\) (5 kPa), i.e. when point \(B\) moves past the normal point \(n\) in Fig. 6, the oxygen consumption rate decreases and the mixed venous \(pO_2\) increases unless the cardiac output and/or the oxygen extraction tension increase as compensation. A decrease in oxygen consumption rate below the optimal level results in glycolysis and lactic acidosis. The cause of Class B hypoxia is "dyserfusion", including increased arterio-venous shunting (\(F_{av}\)), interstitial oedema with increased diffusion distance from haemoglobin to mitochondria (\(l\)), and decreased total capillary endothelial area for \(O_2\) diffusion (\(A\)). Histotoxic hypoxia due to inhibition of the cytochromes also cause a primary increase in critical mixed venous \(pO_2\) because the critical cell \(pO_2\) rises. The therapeutic goal, apart from the causal therapy, is to raise the mixed venous \(pO_2\) to supra-normal values.

Class C hypoxia.
The primary disturbance is an increase in basal oxygen requirement with a secondary increase in critical mixed venous \(pO_2\), as illustrated in Fig. 6 by a rise in the critical point from \(A\) to \(C\). If the cardiac output is unaltered, the mixed venous \(pO_2\) decreases as a result of the increase in \(nO_2\) and the actual point moves from \(n\) to \(e\) in Fig. 6. If the critical point rises above point \(e\), glycolysis and lactic acidosis develop. The causes of Class C hypoxia are hypermetabolism due to uncoupling of the oxidative phosphorylation of ATP or increased ATP requirements. The therapeutic goal is to raise the mixed venous
$pO_2$ eventually to supra-normal values in order to ensure an oxygen diffusion flux which matches the increased $O_2$ consumption rate.

**CONCLUSIONS**

It is important in intensive care to make a causal diagnosis of tissue hypoxia even though a quantitative measure of most of the possible causes is unavailable.

Maintenance of a normal mixed venous $pO_2$ is essential to ensure a normal oxygen diffusion gradient from erythrocytes to mitochondria. This is normally achieved by maintaining a normal cardiac output and a normal arterial oxygen extraction tension. A decreased cardiac output may be compensated by a supra-normal oxygen extraction tension, and vice versa.

In some cases of tissue hypoxia it is necessary to provide a supra-normal mixed venous $pO_2$: In class B hypoxia, to overcome oxygen diffusion problems or cytochrome inhibition, in class C hypoxia, to meet the demands for increased oxygen consumption.

**ALPHABETICAL LIST OF SYMBOLS**

- $A$, $A_{\text{diffus}}$: Total surface area for trans-capillary oxygen diffusion
- $\alpha O_2$: Solubility coefficient for oxygen
- $c_{\text{Hb}}$: Concentration of effective haemoglobin (in blood)
- $c_{\text{Lac}}$: Concentration of lactate (in blood)
- $c_{\text{tO}_2a}$: Concentration of total oxygen in arterial blood
- $c_{\text{tO}_2v}$: Concentration of total oxygen in mixed venous blood
- $D_{\text{ctO}_2a}\text{v}$: Difference in conc. of total oxygen between arterial and mixed venous blood
- $D O_2$: Diffusion coefficient for oxygen
- $d_{\text{pO}_2/dl}$: Differential quotient of $pO_2$ as a function of $l$ (diffusion length)
- $E_{\text{rO}_2}$: Energy rate from $O_2$ combustion divided by body surface area
- $F_{\text{av}}$: Fraction of arterial blood in mixed venous blood (=a-v shunting)
- $\kappa_{O_2}$: Permeability coefficient for oxygen
- $l$, $l_{\text{diffus}}$: Mean length of diffusion (of $O2$ from haemoglobin to mitochondria)
- $n_{\text{ATPglyc}}$: Substance rate of $O2$ divided by body surface area
- $n A_{\text{ATPglyc}}$: Substance rate of adenosine triphosphate glycolytic synthesis
nATPhydrol Substance rate of adenosine triphosphate hydrolysis
nATPox Substance rate of adenosine triphosphate oxidative synthesis
nGlycol Substance rate of glycolysis
nO2diff Substance rate of oxygen diffusion (from haemoglobin to mitochondria)
nO2extr Substance rate of oxygen extraction from blood
nO2flow Substance rate of oxygen flow in blood = oxygen delivery
nO2red Substance rate of oxygen reduction (in mitochondria)
pO2a Tension of oxygen in arterial blood
pO2cap Tension of oxygen in end capillary blood
pO2cell Tension of oxygen in cell cytosol
pO2v Tension of oxygen in mixed venous blood
p50 Extraction tension (of oxygen in arterial blood) = partial pressure of oxygen in arterial blood after extraction of a standard amount of oxygen (2.3 mmol/L)
pO2a Tension of oxygen in arterial blood
VB Volume rate of blood (leaving left ventricle) = cardiac output
VbO2 Volume rate of O2 divided by body surface area

REFERENCES


Address:
Ole Siggaard-Andersen, M.D., Ph.D.
Department of Clinical Biochemistry
University of Copenhagen
Herlev Hospital
DK-2730 Herlev