Acta Anaesthesiol Scand 1995: 39: Supplementum 107, 137-142

Classes of tissue hypoxia

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

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).

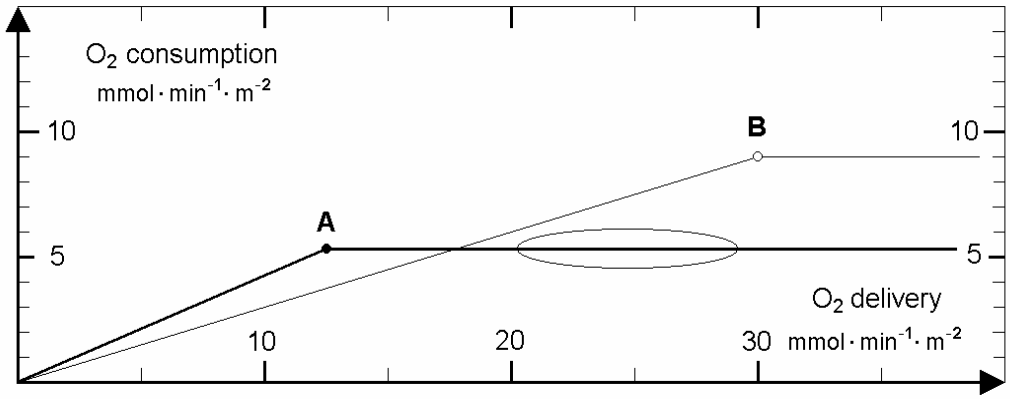

Fig. 1. Oxygen consumption rate as function of oxygen delivery, both relative to body surface area. Below the critical oxygen delivery the oxygen consumption rate becomes delivery dependent and decreases linearly. **A** is the normal critical point. **B** exemplifies a state of critical illness with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

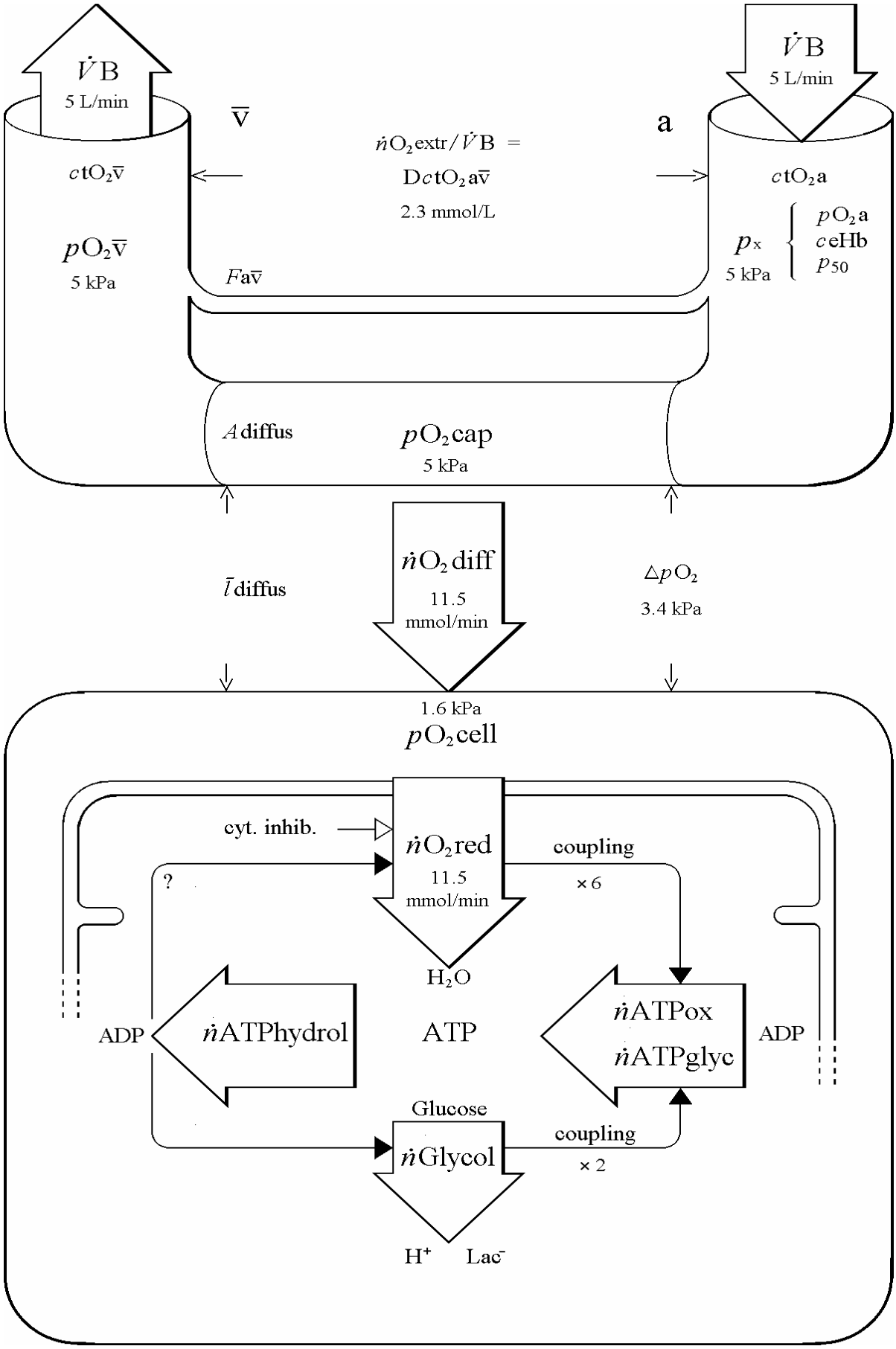

Fig. 2. Schematic model of oxygen transport and reduction. The numbers are representative for a normal 70 kg adult. For explanation see text and alphabetical list of symbols.

Oxygen convection:

The substance rate of oxygen convection in the blood stream, the "oxygen delivery" (nO_2flow), is the product of cardiac output (VBflow) and concentration of total oxygen in the arterial blood (ctO_2a): $nO_2\text{flow} = V\text{Bflow} \cdot ctO_2\text{a}$. The rate of oxygen extraction from the blood (nO_2extr) is the product of cardiac output and arterio-venous total oxygen concentration difference ($DctO_2$av): $nO_2\text{extr} = V\text{Bflow} \cdot DctO_2\text{av}$.

Oxygen diffusion:

The substance rate of oxygen diffusion from haemoglobin to cytochrome aa_3, (nO_2diff), may be derived as the product of the diffusion coefficient (DO_2), the solubility coefficient (αO_2), the total capillary endothelial diffusion area (A), and the oxygen tension gradient (dpO_2/dl): $nO_2\text{diff} = DO_2 \cdot \alpha O_2 \cdot A \cdot dpO_2/dl$. The product of diffusion coefficient and solubility coefficient is the permeability coefficient (κO_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_2cap - pO_2cell) 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_2diff) and extraction (nO_2extr) adjust themselves to match the rate of oxygen reduction, nO_2red. 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.

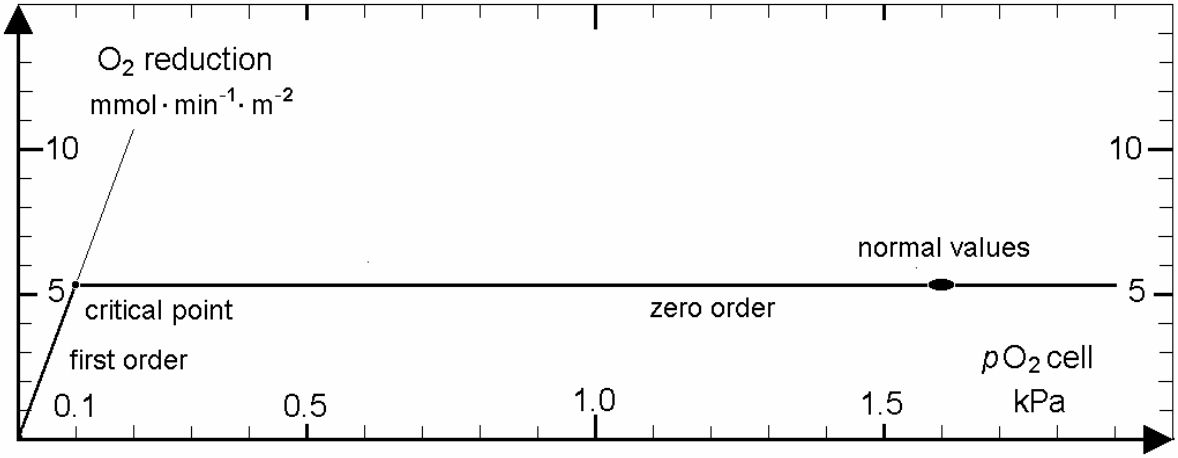

Fig. 3. Oxygen reduction rate as function of cell pO_2. Oxygen reduction is a zero order reaction when cell pO_2 is above a critical value of about 0.1 kPa. Below that value, oxygen reduction becomes a first order reaction with a rate proportional to the cell pO_2. The normal average cell pO_2 is about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

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

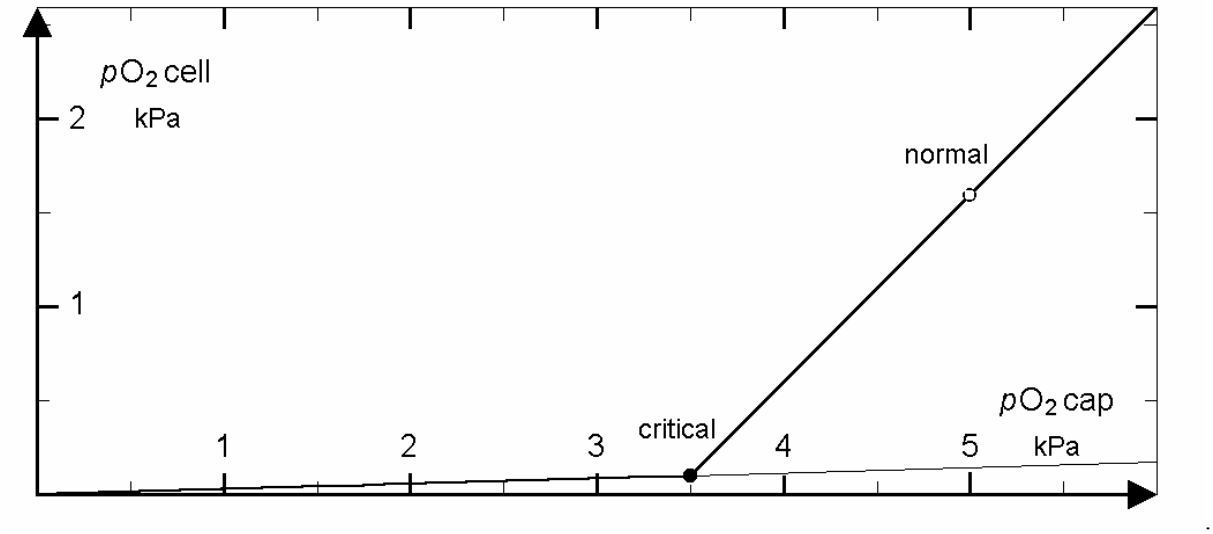

Fig. 4. Relationship between end capillary pO_2 and cell pO_2. Above the critical pO_2 the two are related with a slope of one.

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.

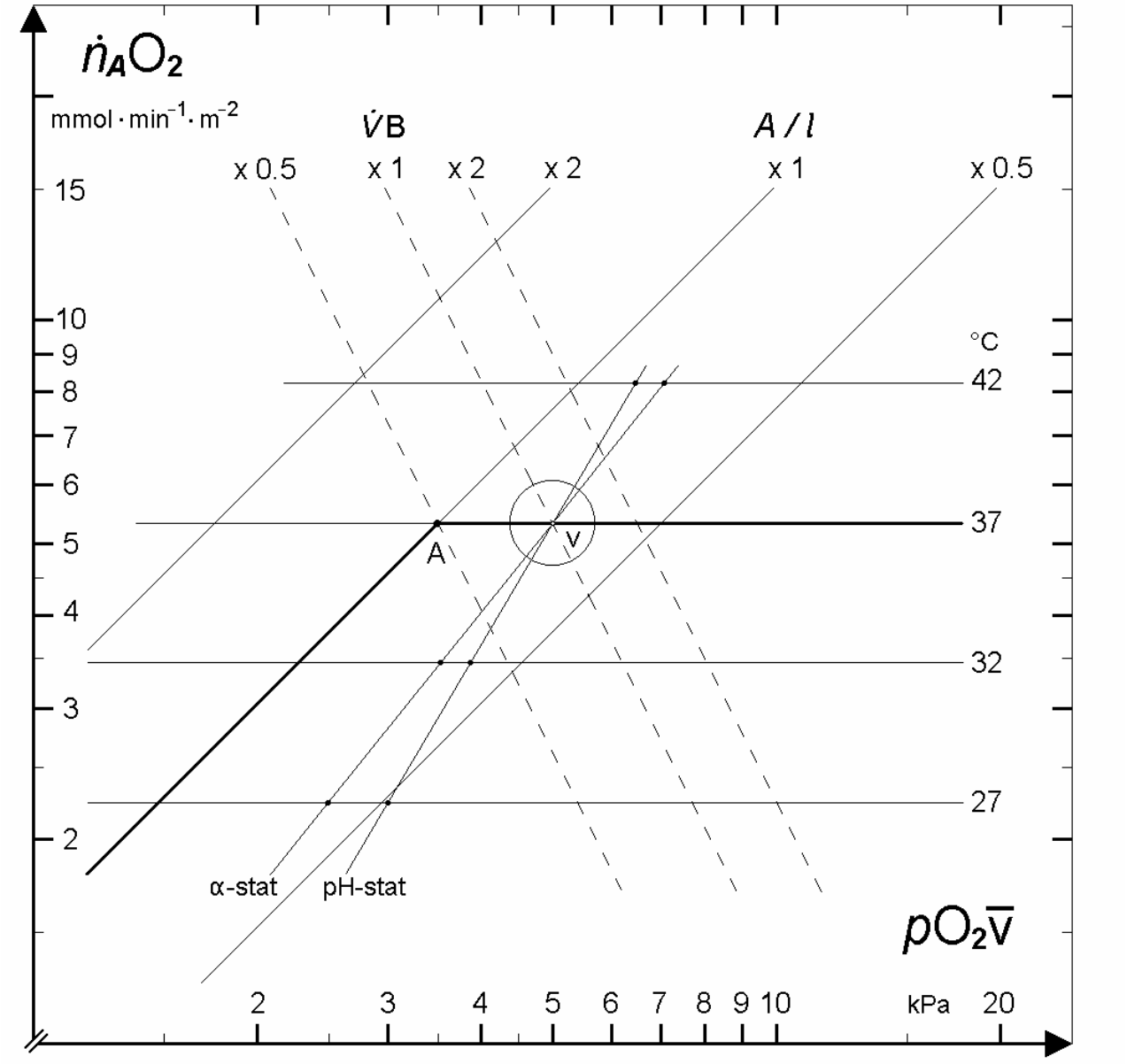

Fig. 5. Relationship between mixed venous pO_2 and oxygen reduction rate related to body surface area in a double logarithmic plot. The circle indicates normal values for a 70 year old man. The heavy line shows the relationship when the mixed venous pO_2 is the independent variable. **A** is the critical 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 α-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 (*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 (*l*diffus) causes *dysperfusion hypoxia*.
5. Decreased endothelial diffusion area for oxygen (*A*diffus) also causes *dysperfusion 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.

EFFECTS				**CAUSES**	
Hypoxia class	Optimal oxygen consumption rate	Critical mixed venous *p*O2	Actual mixed venous *p*O2	**Hypoxia type**	Primary disturbance
A	normal	normal	decrease	*ischemic h.* *low-extractivity h.* - *hypoxemic h.* - *anaemic h.* - *high-affinity h.*	low *V*B low p_x - low pO_2a - low *c*eHb - low p_{50}
B	normal	increase	increase	*shunt h.* *dysperfusion h.* *histotoxic h.*	high *F*av high *l*diffus, low *A*diffus cytochrome inhibition
C	increase	increase	decrease	*ATP-uncoupling h.* *hypermetabolic h.*	low *n*ATPox/nO_2red high nO_2red

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 "dysperfusion", 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 increases. 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 **c** in Fig. 6. If the critical point rises above point **c**, 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.

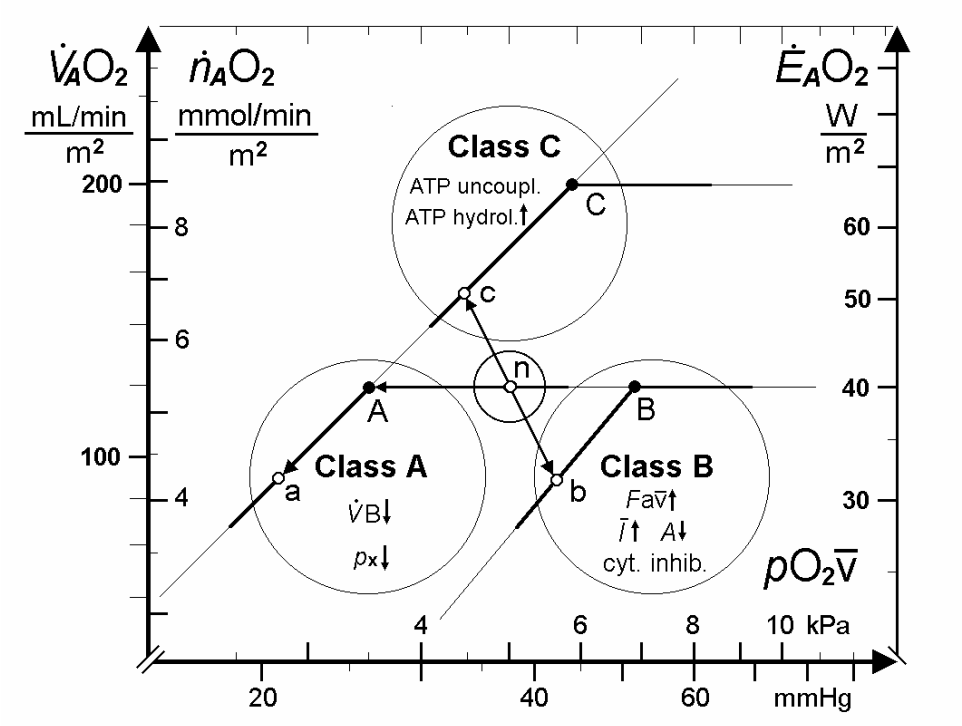

Fig. 6. Illustration of the three classes of tissue hypoxia, class A, B, and C. The circle **n** is the normal area, the centre of which is a normal pO_2v (5 kPa) and a normal (optimal) basal oxygen consumption rate, n_AO_2 (5.3 mmol min^{-1} m^{-2}) or E_AO_2 (40 W m^{-2}). Point **A** indicates the normal critical mixed venous pO_2 of 3.5 kPa. Point **B** exemplifies a situation with a primary increase in critical mixed venous pO_2 but a normal optimal oxygen consumption rate. Point **C** exemplifies a situation with a primary increase in optimal oxygen consumption rate with a secondary increase in critical mixed venous pO_2.

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, Adiffus.	Total surface area for trans-capillary oxygen diffusion
αO_2	Solubility coefficient for oxygen
ceHb	Concentration of effective haemoglobin (in blood)
cLac$^-$	Concentration of lactate (in blood)
ctO_2a	Concentration of total oxygen in arterial blood
ctO_2v	Concentration of total oxygen in mixed venous blood
DctO_2av	Difference in conc. of total oxygen between arterial and mixed venous blood
DO_2	Diffusion coefficient for oxygen
dpO_2/dl	Differential quotient of pO_2 as a function of l (diffusion length)
E_AO_2	Energy rate from O2 combustion divided by body surface area
$Fa\bar{v}$	Fraction of arterial blood in mixed venous blood (=a-v shunting)
κO_2	Permeability coefficient for oxygen
l, $l$diffus	Mean length of diffusion (of O2 from haemoglobin to mitochondria)
n_AO_2	Substance rate of O2 divided by body surface area
nATPglyc	Substance rate of adenosine triphosphate glycolytic synthesis

*n*ATPhydrol	Substance rate of adenosine triphosphate hydrolysis
*n*ATPox	Substance rate of adenosine triphosphate oxidative synthesis
*n*Glycol	Substance rate of glycolysis
nO_2diff	Substance rate of oxygen diffusion (from haemoglobin to mitochondria)
nO_2extr	Substance rate of oxygen extraction from blood
nO_2flow	Substance rate of oxygen flow in blood = oxygen delivery
nO_2red	Substance rate of oxygen reduction (in mitochondria)
pO_2a	Tension of oxygen in arterial blood
pO_2cap	Tension of oxygen in end capillary blood
pO_2cell	Tension of oxygen in cell cytosol
pO_2v	Tension of oxygen in mixed venous blood
p_x	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)
p_{50}	Half-saturation tension (of oxygen)
*V*B	Volume rate of blood (leaving left ventricle) = cardiac output
V_AO_2	Volume rate of O2 divided by body surface area

REFERENCES

1. Shoemaker WC. Relation of oxygen transport patterns to the pathophysiology and therapy of shock states. Intensive Care Med 1987: **13**: 230-243.
2. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee T-S. Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 1988: **94**: 1176-1186.
3. Schumacker PT, Cain SM. The concept of a critical oxygen delivery. Intensive Care med 1987: **13**: 223-229.
4. Siggaard-Andersen O, Fogh-Andersen N, Gøthgen IH, Larsen VH. Oxygen status of arterial and mixed venous blood. Crit Care Med 1995; 23: 1284-1293.
5. Siggaard-Andersen O, Siggaard-Andersen M. The oxygen status algorithm: a computer program for calculating and displaying pH and blood gas data. Scand J Clin Lab Invest 1990: **50**, Suppl 203: 29-45.

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