RESPIRATORY GAS EXCHANGE AT LUNGS, GILLS AND TISSUES: MECHANISMS AND ADJUSTMENTS

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SUMMARY

(1) A general model for external gas exchange organs of vertebrates is presented, in which the main parameters are the ventilatory, diffusive and perfusive conductances for O₂ and CO₂. The relevant properties of the external medium (air or water) and of the internal medium (blood) are analysed in terms of capacitance coefficients (effective solubilities) for O₂ and CO₂. The models for the main types of gas exchange organs (fish gills, amphibian skin, and avian and mammalian lungs) are compared in terms of their intrinsic gas exchange efficacy. The adjustments to increased metabolic rate or to hypoxia are achieved by increasing the conductances.

(2) The gas exchange at tissue level is analysed using the Krogh cylinder and a simplified model containing a diffusive and a perfusive conductance. The adjustments to increased load (exercise, hypoxia) consist in both increased local blood flow and in improvement of diffusion conditions (enlargement and recruitment of capillaries).

(3) Some particular features of respiration in transitional (unsteady) states, such as occurring at the beginning of exercise and of hypoxia, are examined. The additional physical variables are the O₂ (and CO₂) stores acting according to their capacitances and partial pressure changes. Delayed increase in O₂ uptake at the beginning of exercise is due to the limited speed of physiological adjustments. The ensuing O₂ debt is energetically covered by anoxidative energy releasing processes (hydrolysis of high-energy phosphates and anaerobic glycolysis). Finally, the reduction of metabolic rate as adjustment to hypoxia is discussed.

INTRODUCTION

The aim of this report is to outline the mechanisms and the adjustments of gas exchange and transport systems in vertebrates, using models suitable for quantitative analysis.

A generalized and highly simplified scheme of the gas exchange and transport system is depicted in Fig. 1. The elements of the gas transport chain are ventilation, medium/blood diffusion, perfusion (circulation), blood/tissue diffusion, and oxidative tissue metabolism. There is a $P_{O_2}$ gradient from inspired gas to tissue cells and an oppositely directed $P_{CO_2}$ gradient, both consisting of $P_{O_2}$ and $P_{CO_2}$ steps, which reflect the resistances to O₂ and CO₂ transfer of the individual links of the gas transport chain.

The factors determining the individual partial pressure steps are analysed using the
Fig. 1. Simplified schematic model of the respiratory gas exchange and transport system in vertebrates. The individual transport processes are identified and their combinations in external and tissue gas exchange are visualized. Also the $P_{O_2}$ and $P_{CO_2}$ levels at the various sites are qualitatively represented. insp. and exp. denote inspired and expired medium; art. and ven., arterial and venous blood; tis., tissue.

simplest possible models. First, the external gas exchange occurring in various types of gas exchange organs, with air or water as external respiratory medium, is considered. Then the internal (tissue) gas exchange is discussed, using simple models for interaction of blood flow and diffusion. Finally some physiologically important phenomena which occur during transition from one steady state to another (from rest to exercise, from normoxia to hypoxia) are analysed.

A complete coverage of the pertinent literature is impossible in this brief account of a wide research area. Therefore, only a very restricted, personally biased, reference list is appended. More detailed references to the literature can be found in recent reviews by White (1978), Wood and Lenfant (1979a) and Dejours (1981).

I. EXTERNAL GAS EXCHANGE

In this section, emphasis will be placed on the comparative aspects of the function of gas exchange organs in vertebrates. More detailed accounts have been published elsewhere (Piiper & Scheid, 1977; Piiper & Scheid, 1981).

(A) General model

In gas exchange organs of vertebrates the external respiratory medium (air or water) is brought into intimate contact with the internal gas transport medium (blood).
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Specific arrangement

Fig. 2. Model for quantitative analysis of the performance of gas exchange organs of vertebrates. \( M_{O_2} \), \( O_2 \) uptake; \( M_{CO_2} \), \( CO_2 \) output; \( \dot{V} \), ventilation; \( Q \), perfusion; \( G_{diff} \), diffusive conductance; \( \beta_m \) and \( \beta_b \), capitance coefficients of medium and blood, respectively; \( P_i, P_e, P_a \), and \( P_v \), partial pressures in inspired medium, expired medium, venous blood and arterialized blood, respectively (\( \beta \) and \( P \) may be applied to both \( O_2 \) and \( CO_2 \)). Specific arrangement refers to the various models shown in Fig. 3.

The respiratory gases, \( O_2 \) and \( CO_2 \), exchange between the two media by diffusion. The quantitative analysis is based on the following quantities and relationships (Fig. 2):

1. **Transfer rate**, e.g. \( O_2 \) uptake, \( M_{O_2} \), and \( CO_2 \) output, \( M_{CO_2} \).
2. **Flow** of the medium or ventilation, \( \dot{V} \), and blood flow or perfusion, \( Q \).
3. **Concentrations**, \( C \), of \( O_2 \) and \( CO_2 \) in the medium and in blood; for mass balance equations, it is appropriate to employ the same definition of concentration in medium and blood, quantity of substance/volume (Piiper et al. 1971).
4. **Partial pressures**, \( P \), of \( O_2 \) and \( CO_2 \); the conventional unit is torr (= mmHg), although the SI unit, kPa, is increasingly used (1 torr = 0.1333 kPa).
5. **Capitance coefficients**, \( \beta \), of the medium and of blood for \( O_2 \) and \( CO_2 \). This quantity, introduced by Piiper et al. (1971), is defined as increment of concentration per increment of partial pressure (\( \beta = \Delta C/\Delta P \)). The dimension is quantity of substance/(volume. pressure). For the gas phase, \( \beta \) is equal for all (ideal) gases, and equal to \( 1/(R.T) \) (\( R \), gas constant; \( T \), absolute temperature). For inert gases in water and blood, and for \( O_2 \) in water, \( \beta \) is equal to physical solubility. For the respiratory gases \( O_2 \) and \( CO_2 \) in blood, \( \beta \) is equivalent to the slope of the (effective) dissociation curves (i.e. plots of concentration vs. partial pressure).
6. **Diffusing capacity**, \( D \) (or transfer factor), is an index of the diffusive conductance of the barrier separating blood from the external medium. It is defined as transfer rate per mean effective partial pressure difference between external medium and blood: \( D = M/(P_m - P_b) \).
7. **Transport equations.** Convective transport of \( O_2 \) or \( CO_2 \) by ventilation and by perfusion, and diffusive transport between the external medium and blood, are de-
scribed by the following relationships (i, inspired medium; e, expired medium, i incoming, venous blood; a, arterialized blood):

\[ M = \dot{V} \cdot (C_i - C_e) = \dot{V} \cdot \beta_m \cdot (P_i - P_e), \quad (1) \]

\[ M = \dot{Q} \cdot (C_a - C_e) = \dot{Q} \cdot \beta_b \cdot (P_a - P_e), \quad (2) \]

\[ M = D/(P_m - P_b). \quad (3) \]

(8) Conductance, \( G \), is defined as transfer rate per effective partial pressure difference; its reciprocal is resistance (\( R \)). The following basic relationships for ventilatory (vent), perfusive (perf), and diffusive (diff) conductances are obtained from the transport equations:

\[ G_{\text{vent}} = \dot{V} \cdot \beta_m = 1/R_{\text{vent}}, \quad (4) \]

\[ G_{\text{perf}} = \dot{Q} \cdot \beta_b = 1/R_{\text{perf}}, \quad (5) \]

\[ G_{\text{diff}} = D = 1/R_{\text{diff}}. \quad (6) \]

For the overall transfer rate the smallest \( G \) (the highest \( R \)) exerts the strongest limiting effect; conversely, a very high value of \( G \) (when \( R \) is small) implies that the respective process is hardly limiting (e.g. \( G_{\text{diff}} \) in mammalian and avian lungs at rest; \( G_{\text{vent}} \) in skin breathing; \( G_{\text{perf}} \) for \( \text{CO}_2 \) in many cases). To increase \( M_{\text{O}_2} \) and \( M_{\text{CO}_2} \), in exercise, the \( G \) values have to be increased. In mammals, typically \( G_{\text{vent}} \) increases in direct proportion to \( M \), and although \( G_{\text{perf}} \) increases, it is less than proportional to \( M \). Thus, \( P_{\text{O}_2} \) decreases and \( P_{\text{CO}_2} \) increases in mixed venous blood. Also \( G_{\text{diff}} \) tends to increase, but to a still lesser extent, so that increased diffusion limitation results.

(B) External medium: water v. air breathing

In comparing air and water breathing the capacitance coefficients of the medium, \( \beta_m \) for \( \text{CO}_2 \) and \( \text{O}_2 \), are the decisive factors. For air (gas phase), \( \beta_m \) is equal for all (ideal) gases. For water, \( \beta \) for \( \text{O}_2 \) and \( \text{CO}_2 \) are markedly different, the ratio \( \beta_{\text{CO}_2}/\beta_{\text{O}_2} \) being about 30 (the exact figure is dependent on temperature, salinity and buffering). The ratio \( \beta \) (water)/\( \beta \) (gas) is close to unity for \( \text{CO}_2 \), but only about 0.033 for \( \text{O}_2 \). These relationships have the following consequences for external gas exchange (Rahn, 1966; Dejours et al. 1970; Dejours, 1972).

(1) To achieve the same \( \text{O}_2 \) uptake (more precisely, the same \( G_{\text{vent}} \) for \( \text{O}_2 \)), water breathers must ventilate much more than air breathers.

(2) Since \( \beta_{\text{CO}_2} \) is about equal for water and air, the increased ventilation with water breathing means an equally increased \( G_{\text{vent}} \) for \( \text{CO}_2 \), whereby \( P_{\text{CO}_2} \) is markedly diminished in expired water and in arterial blood. This is the reason for the large discrepancy in arterial \( P_{\text{CO}_2} \) between mammals (about 40 torr) and fish (about 1-4 torr).

(3) According to the Henderson–Hasselbalch equation

\[ \text{pH} = pK' + \log \frac{[\text{HCO}_3^-]}{\alpha_{\text{CO}_2} \cdot P_{\text{CO}_2}} \quad (7) \]

(\( pK' \), apparent acid dissociation constant of \( \text{CO}_2 \); \( \alpha_{\text{CO}_2} \), physical solubility of \( \text{CO}_2 \)) a much higher pH is expected in water-breathing animals as compared to air breathers. In reality, however, there is little difference in blood pH between air and water breathers (when compared at the same temperature), because the apparent hyper-
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Ventilation in water breathers is quantitatively compensated by decreased blood bicarbonate concentration (Howell et al. 1970; Reeves, 1977; Reeves & Rahn, 1979).

For the ideal models, $\beta$ is the only significant property of the medium with respect to gas transfer. In real gas exchange organs, however, a number of other properties are important. These are:

1. **Diffusion** properties, characterized by the diffusion coefficient, $d$, or Krogh's diffusion constant, $K (= d \alpha)$, determine the development of partial pressure gradients within the medium (interlamellar water in fish gills; surrounding air or water in skin breathing; 'stratification' in mammalian lungs).

2. **Viscosity**, $\eta$ is a major determinant of the mechanical resistance to respiratory medium flow, both with air and water breathing.

3. **Density**, $\rho$, determines the inertia of the medium and is, therefore, of importance in respiratory flow varying with time within the respiratory cycle.

Since $K$ is much smaller, and $\eta$ and $\rho$ are much higher in water than in air, water breathing is generally more costly, (i.e. requires more energy per volume of medium respired, than does air breathing).

(C) **Medium/blood exchange: diffusion**

In both skin and lungs gas exchange takes place between a homogeneous medium and blood flowing through a dense capillary network. There are, however, two important differences:

1. In lungs the medium is alveolar gas, the composition of which differs from atmospheric air according to transfer rates and $G_{vent}$. The alveolar–capillary barrier is very thin and the surface area is large. Therefore $G_{diff}$ is high, in first approximation not limiting $O_2$ uptake and $CO_2$ output.

2. In amphibian skin the medium is atmospheric air or water. The cutaneous capillary plexus is located beneath the epithelium which has a considerable thickness (to provide protection against mechanical injury and desiccation). Therefore, $G_{diff}$ is low whereas $G_{vent}$ formally approaches infinity. According to Fick's law of diffusion,

$$G_{diff} = d \cdot \alpha \cdot F / \pi$$

($d$, diffusion coefficient; $\alpha$, physical solubility; $F$, surface area; $\pi$, thickness of barrier). The product ($d \cdot \alpha$), termed Krogh's diffusion constant, is about 25 times higher for $CO_2$ than for $O_2$ (mainly due to the differences in $\alpha$). Thus, a skin-breathing animal must have a very low $P_{CO_2}$ regardless of the ambient medium. In fact, in a lungless terrestrial salamander (*Desmognathus fuscus*) the $P_{CO_2}$ of arterialized skin blood was estimated at 5 torr (Piiper et al. 1976). Thus in skin breathing, the overall conductance ratio of $O_2$ and $CO_2$, whether in air or in water, is similar to gill-breathing of water with respect to $P_{CO_2} - P_{O_2}$ relationships (Piiper & Scheid, 1977).

In applying the model to the real situation of blood capillaries in gas exchange organs, a number of complicating features must be taken into consideration.

1. Part of the resistance to diffusion is located within the blood (i.e. in the plasma, red cell membrane and within the red cells).

2. Analogously, the medium, particularly when it is water, may offer a resistance to diffusion.
(3) The physico-chemical processes associated with gas exchange in the blood (e.g., combination of O\textsubscript{2} with haemoglobin, dehydration of carbonic acid (bicarbonate) to CO\textsubscript{2}, exchange of bicarbonate and chloride ions between red cells and plasma) may be rate-limiting.

Values of \( D \) derived from physiological measurements contain all these resistances to O\textsubscript{2} or CO\textsubscript{2} transfer. Because of reaction limitation, the less specific term 'transfer factor' may be preferable to the conventional term 'diffusing capacity'.

(D) Internal transport medium: blood

Of decisive importance, for the transport of both O\textsubscript{2} and CO\textsubscript{2} by blood, is the increase of the 'effective solubility' (measured by the capacitance coefficient (\( \beta_b \))) by reversible chemical combination as O\textsubscript{2}-haemoglobin and as bicarbonate, respectively.

**Oxygen.** The capacitance coefficient \( \beta_b \) for O\textsubscript{2} is largely proportional to the concentration of haemoglobin (O\textsubscript{2} capacity) but varies with \( P_{O_2} \), according to the shape of the O\textsubscript{2} dissociation curve (= plot of O\textsubscript{2} saturation of blood against \( P_{O_2} \)). The shape of the O\textsubscript{2} dissociation curve in turn is determined by the chemical structure of haemoglobin, temperature, pH and \( P_{CO_2} \) (= Bohr effect), and by the intraerythrocyte concentration of organic phosphates (adenosine triphosphate, guanosine triphosphate, 2,3-diphosphoglycerate, inositolpentaphosphate) and of other substances (Cl\textsuperscript{-}, HCO\textsubscript{3}\textsuperscript{-}) functioning as specific regulators of O\textsubscript{2} affinity. The effects and mechanisms are analysed in several recent reviews (e.g. Bauer, 1974; Bartels & Baumann, 1977; Wood & Lenfant, 1979).

**Carbon dioxide.** The \( \beta_b \) value for CO\textsubscript{2} results mainly from reversible formation of bicarbonate with increasing \( P_{CO_2} \), by the buffering action of haemoglobin, plasma proteins and phosphates. Effects are exerted by temperature, the acid-base status and the O\textsubscript{2} saturation of haemoglobin (= Haldane effect).

Both \( \beta_{O_2} \) and \( \beta_{CO_2} \) depend upon the respective partial pressures, according to the slope of the blood dissociation curves. For perfusive transport it is sufficient to use the slope of the straight line crossing the dissociation curve at the arterial and venous values. For calculation of medium-blood transfer, however, particular step-by-step techniques may be required to account for the curvature (Bohr integration). In most instances \( \beta_{CO_2} \) is considerably higher than \( \beta_{O_2} \), and the range of variation of \( P_{CO_2} \) in blood (and in tissue) is much less than that of \( P_{O_2} \).

With the simultaneous circulatory transport of O\textsubscript{2} and CO\textsubscript{2} in opposite directions, both \( \beta_{O_2} \) and \( \beta_{CO_2} \) are increased by the Bohr and Haldane effects, respectively. In hypoxia and in exercise \( \beta_{O_2} \) is increased due to lowering of mean blood \( P_{O_2} \). This property provides an automatic adjustment of \( G_{pert} \) to the challenged O\textsubscript{2} transport system.

(E) Various gas exchange organs: structure and function

The functional properties of gas exchange organs of vertebrates – gills, skin and lungs – can be described in terms of four models illustrated in Fig. 3 (Piiper & Scheid, 1972, 1975).
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Fish gills
- Secondary lamellae
- Blood capillaries
- Ventilatory water flow

Bird lung
- Parabronchus
- Blood capillaries
- Ventilatory air flow

Mammalian lung
- Alveolus
- Ventilation
- Blood capillaries

Amphibian skin
- Skin surface
- Blood capillaries

Fig. 3. Schematic representation of the four fundamental types of vertebrate respiratory organs and their gas exchange performance. From top to bottom: schematized anatomy, models, and partial pressure profiles (P_{O_2} increases upwards, P_{CO_2} increases downwards).

(1) Fish gills
The rows of secondary lamellae carried by the gill filaments form a fine sieve for respiratory water. Gas exchange takes place in the blood lacunae of the secondary lamellae which receives venous blood from the ventral aorta and whose arterialized outflow is into the arterial system. The anatomical arrangement is such that water and blood flows are in opposite directions (counter-current model).

(2) Amphibian skin
Skin breathing is important in all extant amphibians being the only means of gas exchange in those salamanders (terrestrial and aquatic) which possess neither lungs nor gills. Gas exchange takes place in the dense subepithelial capillary network, the inflow to which is in part from the arterial system, in part from a branch of the pulmonary arch carrying venous blood. The oxygenated cutaneous blood flows into the venous system. This is in contrast to the arrangement of pulmonary outflow in tetrapods and lungfish which allows (complete or partial) separation of oxygenated from venous blood.

(3) Bird lungs
The lungs are formed by a number of parabronchi (or tertiary bronchi), in parallel arrangement, most of which connect the mediodorsal secondary bronchi with the
medioventral secondary bronchi. Air passes through the parabronchi, both during inspiration and expiration, in the major part of the lungs unidirectionally, in a smaller part (neopulmo) bidirectionally. Gas exchange takes place in the peri-parabronchial tissue consisting of an interwoven air capillary and blood capillary network. The simplest adequate model for gas transfer in avian lungs is the serial multi-capillary or cross-current model (Scheid & Piiper, 1972; Scheid, 1979).

(4) Mammalian lungs

The airways of mammalian lungs constitute a highly branching system of several orders of bronchi, leading to bronchi carrying alveoli and lastly to alveolar ducts the walls of which are entirely made up by alveoli surrounded by a blood capillary network. Since the renewal fraction of alveolar gas per breath is small, the variations in the composition of alveolar gas are relatively small, and for a simplified analysis a constant composition of alveolar gas may be assumed (ventilated pool model).

The same functional model may be used for the lungs of amphibians and some reptiles. However, in lungs of other reptiles there is a marked tendency to develop non-alveolated regions resembling avian air sacs (Duncker, 1978), which requires a modified cross-current model.

(5) Comparison of models: gas exchange efficacy

The decisive parameter for the overall gas exchange performance of a gas exchange organ, or its model, is the total conductance, \( G_{\text{tot}} = \frac{M}{(P_i - P_e)} \). A comparison of \( G_{\text{tot}} \) for the various models yields the picture shown in Fig. 4. The following decreasing order of gas exchange efficiency is obtained for the models (the 'infinite pool' model is a limiting case resulting from all models when \( G_{\text{vent}} \) approaches infinity):

\[
\text{counter-current} > \text{cross-current} > \text{ventilated pool}.
\]

Fig. 4 shows also that the differences in efficiency between the models are largest with good diffusing conditions (\( G_{\text{diff}} \) large to infinity).

The gas exchange efficacy in real gas exchange organs is considerably less than in idealized models due to functional inhomogeneities, dead space, vascular shunts and other factors (Piiper & Scheid, 1977).

The reason for the adoption of a certain type of gas exchange organ by the different vertebrate groups cannot be sought in the gas exchange requirements alone. Nevertheless, the following may be stated.

(1) As water-breathing is energetically costly (see above), it is important for fishes to use the scarce dissolved \( O_2 \) as effectively as possible. This is achieved by the counter-current strategy.

(2) Birds, many of which are capable of sustained flight at high altitudes, require particularly efficient gas exchange organs. However, the higher tolerance of hypoxia by birds as compared to mammals probably results from other, unknown, factors besides the efficient cross-current type gas/blood arrangement in lungs.

(6) Adjustments

Physiologically important adjustments are made (1) to increased metabolism, (2) to changes in the respiratory medium, and (3) to disturbances by disease.
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Fig. 4. Comparison of gas transfer efficacies of three models. Abscissa: resistance to diffusion, equal to the reciprocal of diffusive conductance \( G_{\text{diff}} \). Ordinate: total conductance \( G_{\text{tot}} = \frac{M}{(P_{1} - P_{2})} \). All conductances are standardized to \( G_{\text{vent}} \) and \( G_{\text{perf}} \), both constant at 1.0 units.

1. In exercise the conductances are increased. In man and mammals, \( G_{\text{vent}} \) (i.e. \( V \)) increases proportionally to \( M_{O_{2}} \) and \( M_{CO_{2}} \) by increasing both tidal volume and breathing frequency. \( G_{\text{perf}} \) also rises, due to increased cardiac output, \( Q \), brought about by increased cardiac frequency and stroke volume, but also due to increase of \( \beta_{O_{2}} \) of blood produced by lowering of venous \( P_{O_{2}} \) and by increase of blood haematocrit. The extent of increase of \( G_{\text{diff}} \) is unclear, and its extent is probably rather limited. Therefore, the role of diffusion limitation is expected to increase in exercise. The adjustments seem to be similar in birds (cf. Fedde, 1976; Bouverot, 1978) and in fish (cf. Randall, 1970; Johansen, 1971).

2. Similar adaptive changes occur during environmental hypoxia. However, since only the \( O_{2} \) availability is reduced, the hyperventilation must lead to hypocapnia, which may be compensated by adjustment of the bicarbonate concentration in blood. In environmental hypercapnia, increased \( G_{\text{vent}} \) alleviates the acidosis. In water-breathing animals, however, even a large increase in \( G_{\text{vent}} \) would have little effect, and the main adjustment observed is increase of blood bicarbonate leading to compensation of the respiratory acidosis (Heisler, 1980).

3. The compensations for anatomical and functional derangements in the respiratory gas transport system in various diseases are not only of interest for clinical physiology, but also contribute to the understanding of the basic mechanisms involved. Examples of such compensatory mechanisms include increased ventilation of lungs with impaired gas exchange function, renal compensation of respiratory acidosis due to disturbed lung function, increased cardiac output in anaemia, and hypoxic vasoconstriction in lung regions with airway obstruction.
II. TISSUE GAS EXCHANGE

The quantitative analysis of O\textsubscript{2} and CO\textsubscript{2} exchange in tissues is less advanced than that in external gas exchange organs, due mainly to the experimental difficulties involved in determining P\textsubscript{O\textsubscript{2}} and P\textsubscript{CO\textsubscript{2}} in tissues and also due to problems of adequate modelling (cf. Tenney, 1974; Grunewald & Sowa, 1977).

In tissue respiration usually only O\textsubscript{2} is considered. The main reason for this derives from the existence of an absolute limit for tissue P\textsubscript{O\textsubscript{2}} (P\textsubscript{O\textsubscript{2}} = 0), whereas no such limit exists for P\textsubscript{CO\textsubscript{2}}. Moreover, all P\textsubscript{CO\textsubscript{2}} gradients are small, because of high β and high K for CO\textsubscript{2} (equation 8).

(A) Models

(1) Krogh's cylinder

The most widely used model for analysis of tissue O\textsubscript{2} supply is the Krogh cylinder (Krogh, 1919) which displays a radial and a longitudinal (arterio-venous) P\textsubscript{O\textsubscript{2}} gradient (Fig. 5A). For the total radial P\textsubscript{O\textsubscript{2}} difference (i.e. the difference between P\textsubscript{O\textsubscript{2}} in the axial capillary blood) P\textsubscript{c} and P\textsubscript{O\textsubscript{2}} at the surface of the cylinder, P\textsubscript{0}, in any cross-sectional segment of the cylinder, the following equation is obtained assuming, (1) homogeneous distribution of O\textsubscript{2} consumption to tissue volume, (2) uniform diffusivity (K), and (3) no longitudinal diffusion:

\[
P_{c} - P_{0} = \frac{m}{4K} \cdot r_{c}^{2} \left[2 \ln \left(\frac{r_{0}}{r_{c}}\right) + \left(\frac{r_{c}}{r_{0}}\right)^{2} - 1\right]
\]

\(m\), O\textsubscript{2} consumption per tissue volume; \(K\), Krogh’s diffusion constant; \(r_{0}\), radius of tissue cylinder; \(r_{c}\), radius of capillary).

Introducing a specific effective diffusive O\textsubscript{2} conductance, \(d'\),

\[
d' = \frac{4K}{r_{c}^{2} \cdot \left[2 \ln \left(\frac{r_{0}}{r_{c}}\right) + \left(\frac{r_{c}}{r_{0}}\right)^{2} - 1\right]}
\]

one obtains:

\[
P_{c} - P_{0} = \frac{m}{d'}
\]

The longitudinal gradient is the same in blood and in tissue at a given distance from the capillary. The corresponding total longitudinal P\textsubscript{O\textsubscript{2}} difference follows from Fick’s principle:

\[
P_{a} - P_{v} = \frac{m}{\hat{q} \cdot \beta_{b}}
\]

(\(\hat{q}\), perfusion per tissue volume).

For the largest P\textsubscript{O\textsubscript{2}} difference, i.e. between arterial P\textsubscript{O\textsubscript{2}} and P\textsubscript{O\textsubscript{2}} at the periphery of the venous end of the cylinder, P\textsubscript{0(v)}, one obtains by combining eqs. (11) and (12):

\[
P_{a} - P_{0(v)} = \frac{m}{d' + \frac{1}{\hat{q} \cdot \beta_{b}}}
\]

The tissue P\textsubscript{O\textsubscript{2}} in Krogh cylinder is rather varied, extending from arterial P\textsubscript{O\textsubscript{2}} to values lower than venous P\textsubscript{O\textsubscript{2}}. The volume-averaged mean P\textsubscript{O\textsubscript{2}} is usually near venous P\textsubscript{O\textsubscript{2}} (Tenney, 1974).
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Fig. 5. Models for analysis of O₂ transfer in tissues. The lower panels show schematically O₂ partial pressure profiles in the models. (A) Krogh's cylinder with axial blood capillary. \( r_0 \), radius of capillary; \( r_0 \), radius of cylinder, \( q \), blood flow per unit tissue volume. The radial \( P_{O_2} \) profile across the tissue cylinder is shown at the arterial end (from \( P_a \) to \( P_{O_2(a)} \)) in the middle, and at the venous end (from \( P_v \) to \( P_{O_2(v)} \)). The longitudinal profile of \( P_{O_2} \) is represented for the capillary (\( P_2 \)) and for the periphery of the cylinder (\( P_2 \)). (B) Simplified model (total resistance to \( O_2 \) uptake in a thin layer, no \( P_{O_2} \) gradients in tissue). \( P_2 \), \( P_2 \), and \( P_2 \), \( P_2 \), \( P_2 \) in tissue, in arterial and in venous blood, respectively; \( d \), diffusive conductance per unit tissue volume; \( q \), blood flow per unit tissue volume. The longitudinal \( P_{O_2} \) gradient in blood is shown (from \( P_2 \) to \( P_2 \)).

(2) Simplified model

Although Krogh's cylinder is homogeneous with respect to diffusivity and solubility of \( O_2 \), most resistance to diffusion is located near the capillary, because here the \( O_2 \) flux density is highest. Thus no great inaccuracy is introduced when the model is simplified by completely separating the resistance to \( O_2 \) diffusion from the \( O_2 \) consuming tissue compartment, which in the Krogh model is predominantly represented by the more peripheral regions of the cylinder. Furthermore, longitudinal diffusion, which is not permitted in Krogh's model, would reduce the longitudinal \( O_2 \) gradient. Moreover, when adjacent parallel capillaries are not perfectly aligned, but overlap, and when their blood flow is in part counter-current, the mean tissue \( P_{O_2} \) is expected to show less pronounced longitudinal \( O_2 \) gradients.

It is, therefore, of interest to consider a model with uniform tissue \( P_{O_2} \) as an alternative of Krogh's cylinder (Fig. 5B). The tissue is separated from the capillary blood flow by a diffusion-resistive layer, functionally characterized by a specific diffusive conductance (diffusing capacity) per unit tissue volume, \( d \).

\[
d = K \cdot f \cdot 1 / x
\]

(14)

(\( f \), effective barrier surface area per unit tissue volume; \( x \), effective barrier thickness; \( K \), Krogh's diffusion constant of the barrier).

The following relationship is obtained for the maximum blood–tissue \( P_{O_2} \) difference:

\[
P_a - P_v = \frac{m}{\bar{q} \beta_0 [1 - \exp (-d / (\bar{q} \beta_0))].}
\]

(15)
(B) Adjustments

Both models may be used to investigate the adaptive physiological changes in hypoxia (reduction of arterial $P_{O_2}$) and in activity (increased tissue $O_2$ consumption) which maintain tissue $P_{O_2}$ at an adequate level for oxidative metabolic demands. Clearly the adaptive changes must affect either the circulatory $O_2$ supply by the blood (specific tissue blood flow, $\dot{q}$, and the capacitance coefficient of blood for $O_2$, $\beta_b$) or the blood–tissue diffusion characteristics, as quantified in terms of the specific diffusing capacity ($d$ or $d'$).

(1) Blood (perfusive conductance)

Increase in tissue blood flow, $\dot{q}$, is an effective means of increasing tissue $O_2$ supply. At high blood flows or, more precisely, at high $\dot{q}/d$ or $\dot{q}/d'$ values a further increase in $\dot{q}$ becomes ineffective, because the $O_2$ supply is then mainly limited by diffusion; this behaviour is evident from eqs. (13) and (15).

Increasing the capacitance coefficient, $\beta_b$, has formally the same effect as increase of $\dot{q} \cdot \beta_b$ may be increased by increase of haematocrit or by change of the slope of the $O_2$ saturation – $P_{O_2}$ relationship, which is increased in hypoxia. Thus the shape of the blood $O_2$ dissociation curve provides an automatic adjustment of perfusive $O_2$ conductance in arterial hypoxia, as well as in venous hypoxia occurring in exercise with increased utilization of blood oxygen.

(2) Tissue diffusion (diffusive conductance)

Physiologically there are two ways to improve diffusion conditions for $O_2$ in tissues.

(a) An increase of the capillary diameter or radius ($r_e$) increases $d'$ in equation (10) and $d$ in equation (14) by increasing the effective surface area available for diffusion.

(b) Opening of closed, unperfused, capillaries increases the capillary density and thereby reduces the effective radius of the $O_2$ supply cylinder ($r_0$ in equation (10)) and the effective diffusion distance ($x$ in equation (14)).

The effectiveness of these measures to increase $O_2$ supply is high when the ratio $d/(\dot{q} \cdot \beta_b)$ or $d'/(\dot{q} \cdot \beta_b)$ is small, meaning predominant diffusion limitation of blood–tissue $O_2$ transfer. With high values of these ratios increased perfusion would be more effective since in these conditions $O_2$ supply is preponderantly perfusion-limited.

(C) Complications in real tissues

In real tissues the simple models may become inadequate for many reasons, two of which will be briefly addressed.

(1) Arrangement in multicapillary systems

In real tissues, even with essentially parallel arrangement of capillaries, like in muscle, complications arise when in adjacent capillaries the arterial and the venous ends are at different levels and the directions of flow are counter-current (cf. Grunewald & Sowa, 1977). The counter-current arrangement leads to a truncated cone model of $O_2$ supply, and appears to provide more efficient $O_2$ supply than a co-current arrangement. However, with high diffusive conductance (dense capillary network) shunting
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of O₂ from the arterial end of one capillary into the venous end of another capillary (or of the same loop-shaped capillary) will occur, whereby the O₂ transport efficiency is decreased.

(2) Inhomogeneity

There is experimental evidence for a rather inhomogeneous distribution of blood flow to volume in apparently homogeneous muscles (e.g. Sparks & Mohrman, 1977). The efficiency of O₂ supply in a system of parallel capillary units with unequal blood flow is reduced because it reaches critical O₂ supply conditions at lower O₂ requirement or at higher total blood flow than in a homogeneously perfused system.

For O₂ supply, it is the distribution of \( \dot{q} \) and \( d \) (or \( d' \)) relative to \( \dot{m} \) which is the important variable, thus one has to consider the \( \dot{m}/\dot{q}/d \) inhomogeneity'. It would be interesting to know if in exercising muscle the \( \dot{m}/\dot{q}/d \) inhomogeneity is reduced by local micro-circulatory control mechanisms (adjustment of blood flow and capillary density to the local metabolic level).

III. GAS TRANSPORT AND METABOLISM IN UNSTEADY STATE

Steady state is an ideal condition, appreciated by physiologists, but never fully achieved in reality. Gas transport clearly varies within a muscle fibre twitch, a cardiac cycle, a respiratory cycle, activity–rest cycle, cyclic changes in environment etc. There is particular interest in the last-mentioned changes which have a longer period and, therefore, can be analysed in terms of transition from one steady state to another.

(A) Capacitance

The important additional variables required for analysis of unsteady states of gas transport are the capacitances, \( B \), defined as change in amount of substance (gas) per change in partial pressure:

\[
B = dM/dP. \quad (16)
\]

The capacitance is proportional to the volume, \( V \), and to the capacitance coefficient, \( \beta \):

\[
B = V\cdot\beta. \quad (17)
\]

Thus the amount of O₂ liberated by lowering of O₂ partial pressure from \( P_1 \) to \( P_2 \) is

\[
M = V\cdot\beta\cdot(P_1 - P_2) = B(P_1 - P_2) \quad (18)
\]

The main capacitances for O₂, or O₂ stores, of the body are lung gas, blood (arterial and venous), tissues (with and without myoglobin). During breath-holding, after lowering of inspired O₂ and after onset of exercise, the O₂ partial pressures in various compartments change, and thereby stored O₂ is released (usually to be promptly consumed) according to the respective capacitances.

(B) Dynamics: delayed change

An imposed step change (e.g. a sudden drop of inspired \( P_{O_2} \), or an abrupt increase in the metabolic rate at the beginning of exercise) causes a delayed change in other
quantities (e.g. arterial $P_{O_2}$ or $M_{O_2}$, respectively) to a new steady state value. This delayed change may be described by a characteristic time, $t_0$,

$$t_0 = \frac{1}{y_2 - y_1} \int_{t_0}^{t \to \infty} (y_2 - y) \, dt$$

($y$, a time-dependent variable, changing from $y_1$ at time = 0 to $y_2$ at time = $\infty$)

In the simplest case this approach to a new equilibrium is exponential:

$$y_2 - y = (y_2 - y_1) \exp \left( -t/\tau \right).$$

In this case $t_0$ is equal to the time constant, $\tau$, which is proportional to the half time, $t_{1/2} (\tau = 0.693 \, t_4)$.

The delay (finite kinetics) may result from two categories of factors.

(1) It may reflect the capacitive/conductive properties of the gas transport system. In the simplest case, $\tau$ is equal to the capacitance/conductance ratio

$$\tau = B/G.$$  

(21)

This behaviour is found in the time course of CO$_2$ release from incubated chicken eggs upon sudden changes in environmental gas, $\tau$ being in accordance with predictions from steady-state CO$_2$ conductance and estimated capacitance of CO$_2$ storage (Tazawa et al. 1981). The same relationship, equation (21), is the basis of the determination of the pulmonary diffusing capacity for CO by the single breath method (Krogh & Krogh, 1909) and of pulmonary diffusing capacities for O$_2$, CO$_2$ and CO, and of pulmonary capillary blood flow from rebreathing equilibration of test gases in lungs (Meyer et al. 1981; Piiper et al. 1980b).

(2) Furthermore, the delay may be due to the slowness of adaptive changes in the gas transport system after an abrupt change of a variable. An important example is the delayed increase of O$_2$ uptake after onset of exercise of constant power. The cause is the time requirement of increase in ventilation, cardiac output, muscle blood flow and diffusing conditions in the muscle (Cerretelli et al. 1980; di Prampero, 1981).

(C) Oxygen debt

An important consequence of delayed increase of $M_{O_2}$ after onset of exercise is the O$_2$ debt (or O$_2$ deficit) (Fig. 6). Assuming constant efficiency of oxidative metabolism, the following amount of O$_2$, $M$, is 'missing' from the balance:

$$M = \int_{t=0}^{t \to \infty} (M_{O_2} - M) \, dt.$$  

($M$, time-dependent O$_2$ uptake; $M_{O_2}$, O$_2$ uptake at steady state of exercise.)

The O$_2$ debt and its energy equivalent are attributed to several mechanisms (Fig. 7):

(1) O$_2$ stores (mainly tissue and venous blood),

(2) energy gained from hydrolysis of high-energy phosphates (ATP and creatine phosphate), and

(3) energy gained from anaerobic glycolysis, leading to accumulation of lactate.

The common denominator for these changes is energy release, oxidative for (1), anoxidative for (2) and (3). The involved energy equivalences have been determined
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Fig. 6. Schema of the behaviour of $O_2$ and other variables during and after a medium exercise of constant power (in a mammal or in an isolated mammalian muscle). From top to bottom: $O_2$ uptake, $M_{O_2}$; change of $O_2$ stores, $\Delta [O_2]$; change of high-energy phosphate concentration, $\Delta [\sim P]$; energy turnover rates, $E$: total energy turnover rate (thick line) and its components (hatched areas); external power, $W$. The equality of $O_2$ debt contracted and repaid is assumed for simplicity; in reality $O_2$ debt repaid is usually higher (cf. Piiper et al. 1980).

Fig. 7. Relationships between $O_2$ uptake, oxidative and an-oxidative energy release, and $O_2$ and high-energy phosphate stores, for analysis of $O_2$ debt. The scheme is not intended to depict the metabolic pathways: ATP is shown only in its energy storage function, not as an obligatory intermediate in energy turnover.
in vivo (cf. Piiper et al. 1980a). It has been shown that the O₂ debt incurred after onset of light or medium exercise is energetically explained by hydrolysis of high energy phosphates, mainly phosphocreatine (Piiper et al. 1968). At least part of the O₂ debt repayment is required for resynthesis of phosphocreatine to the resting level (Piiper & Spiller, 1970).

The relationship between the kinetics of O₂ uptake after onset of exercise with the changes in high-energy phosphates can be considered from two points of view:

(a) A certain metabolic level is associated with a certain degree of hydrolysis of high energy phosphates; the energy released therefrom is utilized for mechanical work and therefore the adjustment of O₂ supply need not be instantaneous.

(b) The adjustments of O₂ supply are intrinsically slow, giving rise to an O₂ debt which has to be covered by splitting of high-energy phosphates.

In any case, the speed of the adjustments and the functional energy stores must be interrelated in a manner to render possible rapid, but economical, energy release.

(D) Depression of metabolism

The O₂ debt associated with exercise of vertebrate muscles is usually repaid during the recovery. After onset of hypoxia, however, in many lower vertebrates the O₂ uptake is reduced, and after return to normoxia there is little overshoot in O₂ uptake: this behaviour is called O₂ conformity, in contrast to O₂ regulation meaning O₂ consumption independent of O₂ supply (cf. Prosser, 1973).

In many cases the O₂ conformity appears not to be only a passive consequence of shortage of O₂ supply, but it should rather be interpreted as an adjustment to reduced O₂ supply. This certainly was the case in lungless salamanders subjected to deep hypoxia, since they showed recovery of initially increased lactate and decreased high energy phosphates during persisting hypoxia and reduced O₂ uptake (Gatz & Piiper, 1979). Similarly, the reduced oxidative metabolism during diving in habitually diving mammals is the result of specific circulatory and metabolic control mechanisms (Andersen, 1966).

Probably there are transitions from O₂-debt repaid fully (or even in excess), through O₂ debt repaid partially to ‘true’ reduced metabolic state. Their systematic and comparative study in lower vertebrates is expected to be rewarding.

REFERENCES

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