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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 O_2 and CO_2. The relevant properties of the exernal medium (air or water) and of the internal medium (blood) are analysed in terms of capacitance coefficients (effective solubilities) for O_2 and CO_2. 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 O_2 (and CO_2) stores acting according to their capacitances and partial pressure changes. Delayed increase in O_2 uptake at the beginning of exercise is due to the limited speed of physiological adjustments. The ensuing O_2 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 O_2 and CO_2 transfer of the individual links of the gas transport chain.

The factors determining the individual partial pressure steps are analysed using the

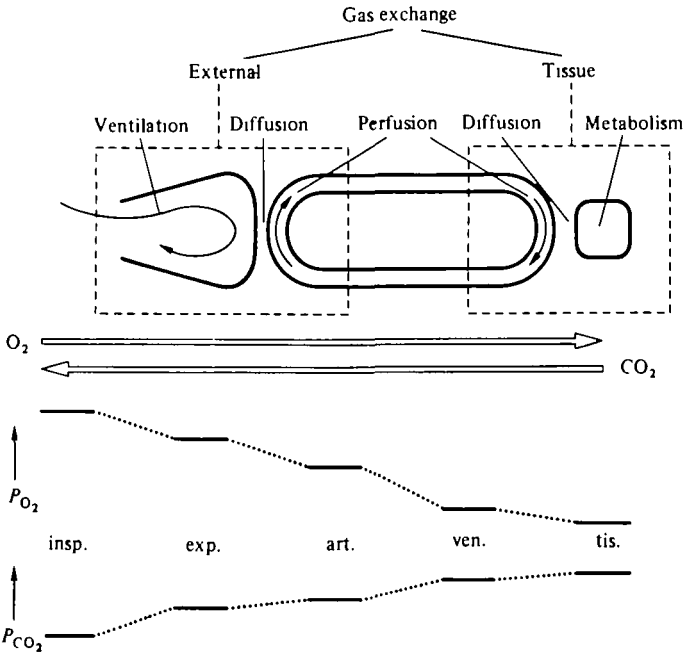

Fig. 1. Simplified schematic model of the respiratory gas exchange and transport system in vertebrates. The individual transport processes are identified and their combinations in external and tissue gas exchange are visualized. Also the P_{O_2} and P_{CO_2} levels at the various sites are qualitatively 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 biassed, reference list is appended. More detailed references to the literature can be found in recent reviews by White (1978), Wood and Lenfant (1979*a*) 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).

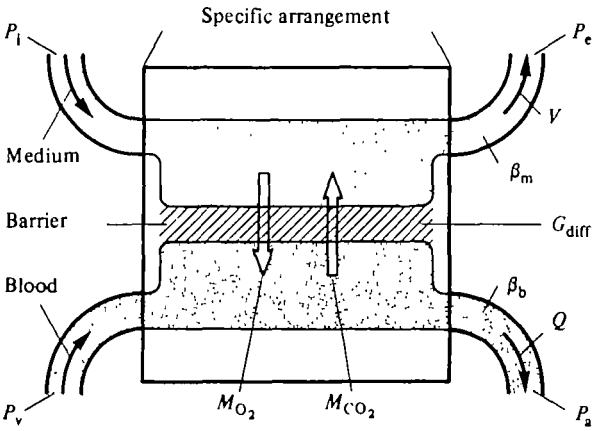

Fig. 2. Model for quantitative analysis of the performance of gas exchange organs of vertebrates. $\dot{M}_{O_2}$, O_2 uptake; $\dot{M}_{CO_2}$, CO_2 output; $\dot{V}$, ventilation; $\dot{Q}$, perfusion; G_{diff}, diffusive conductance; β_m and β_b, capitance coefficients of medium and blood, respectively; P_i, P_e, P_v and P_a, partial pressures in inspired medium, expired medium, venous blood and arterialized blood, respectively (β 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, $\dot{M}_{O_2}$, and CO_2 output, $\dot{M}_{CO_2}$.

(2) *Flow* of the medium or ventilation, $\dot{V}$, and blood flow or perfusion, $\dot{Q}$.

(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) *Capacitance coefficients*, β, 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, β 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, β is equal to physical solubility. For the respiratory gases O_2 and CO_2 in blood, β 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: $D = \dot{M}/(\overline{P_m - P_b})$.

(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, *v*, incoming, venous blood; *a*, arterialized blood):

$$\dot{M} = \dot{V}.(C_i - C_e) = \dot{V}.\beta_m.(P_i - P_e), \tag{1}$$

$$\dot{M} = \dot{Q}.(C_a - C_v) = \dot{Q}.\beta_b.(P_a - P_v), \tag{2}$$

$$\dot{M} = D/\overline{(P_m - P_b)}. \tag{3}$$

(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:

$$G_{vent} = \dot{V}.\beta_m = 1/R_{vent}, \tag{4}$$

$$G_{perf} = \dot{Q}.\beta_b = 1/R_{perf}, \tag{5}$$

$$G_{diff} = D = 1/R_{diff}. \tag{6}$$

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_{diff} in mammalian and avian lungs at rest; G_{vent} in skin breathing; G_{perf} for CO_2 in many cases). To increase $\dot{M}_{O_2}$ and $\dot{M}_{CO_2}$ in exercise, the G values have to be increased. In mammals, typically G_{vent} increases in direct proportion to $\dot{M}$, and although G_{perf} increases, it is less than proportional to $\dot{M}$. Thus, P_{O_2} decreases and P_{CO_2} increases in mixed venous blood. Also G_{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, β_m for CO_2 and O_2, are the decisive factors. For air (gas phase), β_m is equal for all (ideal) gases. For water, β for O_2 and CO_2 are markedly different, the ratio β_{CO_2}/β_{O_2} being about 30 (the exact figure is dependent on temperature, salinity and buffering). The ratio β (water)/β (gas) is close to unity for CO_2, but only about 0·033 for 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 O_2 uptake (more precisely, the same G_{vent} for O_2), water breathers must ventilate much more than air breathers.

(2) Since β_{CO_2} is about equal for water and air, the increased ventilation with water breathing means an equally increased G_{vent} for CO_2, whereby P_{CO_2} is markedly diminished in expired water and in arterial blood. This is the reason for the large discrepancy in arterial P_{CO_2} between mammals (about 40 torr) and fish (about 1–4 torr).

(3) According to the Henderson–Hasselbalch equation

$$pH = pK' + \log \frac{[HCO_3^-]}{\alpha_{CO_2}.P_{CO_2}} \tag{7}$$

(pK', apparent acid dissociation constant of CO_2; α_{CO_2}, physical solubility of 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-

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, β 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*, η is a major determinant of the mechanical resistance to respiratory medium flow, both with air and water breathing.

(3) *Density*, ρ, 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 η and ρ are much higher in water than in air, water breathing is generally more costly, (i.e. requiress 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,

$$G_{diff} = d.\alpha.F/x \tag{8}$$

(d, diffusion coefficient; α, physical solubility; F, surface area; x, thickness of barrier). The product $(d.\alpha)$, termed Krogh's diffusion constant, is about 25 times higher for CO_2 than for O_2 (mainly due to the differences in α). 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_2 with haemoglobin, dehydration of carbonic acid (bicarbonate) to CO_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_2 or CO_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_2 and CO_2 by blood, is the increase of the 'effective solubility' (measured by the capacitance coefficient (β_b)) by reversible chemical combination as O_2-haemoglobin and as bicarbonate, respectively.

Oxygen. The capacitance coefficient β_b for O_2 is largely proportional to the concentration of haemoglobin (O_2 capacity) but varies with P_{O_2} according to the shape of the O_2 dissociation curve (= plot of O_2 saturation of blood against P_{O_2}). The shape of the O_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^-, HCO_3^-) functioning as specific regulators of O_2 affinity. The effects and mechanisms are analysed in several recent reviews (e.g. Bauer, 1974; Bartels & Baumann, 1977; Wood & Lenfant, 1979*b*).

Carbon dioxide. The β_b value for CO_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_2 saturation of haemoglobin (= Haldane effect).

Both β_{O_2} and β_{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 β_{CO_2} is considerably higher than β_{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_2 and CO_2 in opposite directions, both β_{O_2} and β_{CO_2} are increased by the Bohr and Haldane effects, respectively. In hypoxia and in exercise β_{O_2} is increased due to lowering of mean blood P_{O_2}. This property provides an automatic adjustment of G_{perf} to the challenged O_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).

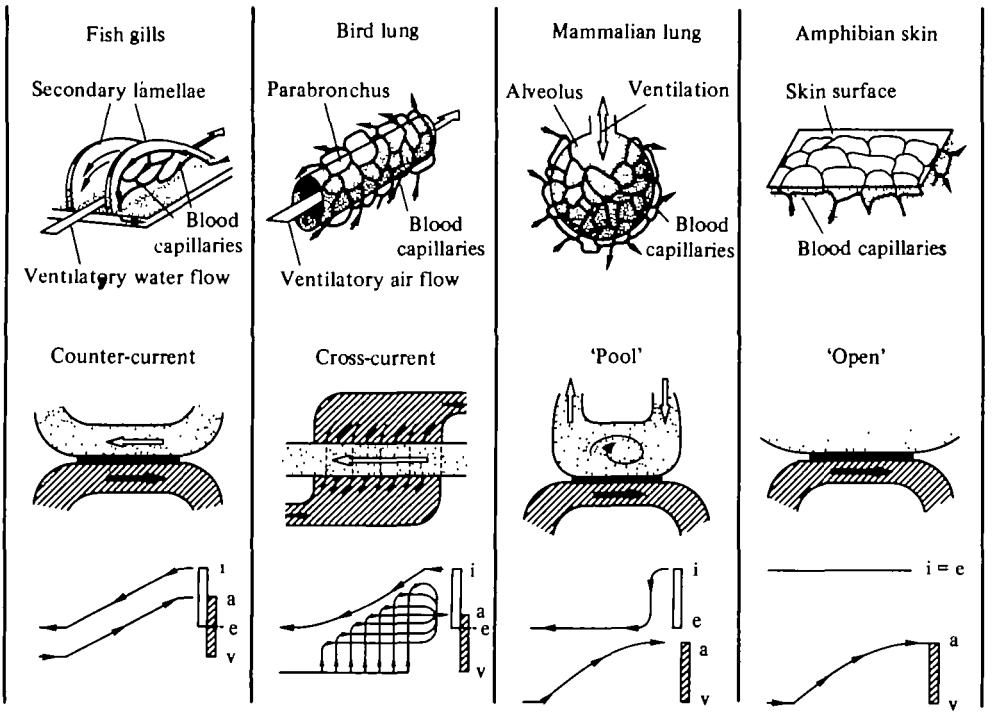

Fig. 3. Schematic representation of the four fundamental types of vertebrate respiratory organs and their gas exchange performance. From top to bottom: schematized anatomy, models, and partial pressure profiles (P_{O_2} increases upwards, P_{CO_2} increases downwards).

(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 slamanders (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, $G_{tot} = \dot{M}/(P_i - P_v)$. A comparison of G_{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_{vent} approaches infinity):

counter-current > cross-current > ventilated pool.

Fig. 4 shows also that the differences in efficiency between the models are largest with good diffusing conditions (G_{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.

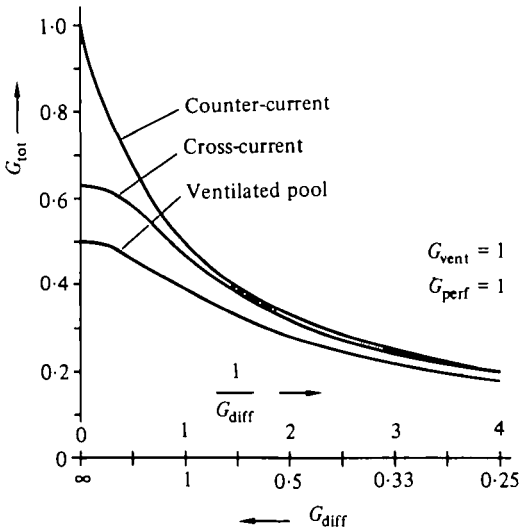

Fig. 4. Comparison of gas transfer efficacies of three models. Abscissa: resistance to diffusion, equal to the reciprocal of diffusive conductance (G_{diff}). Ordinate: total conductance $G_{tot} = \dot{M}/(P_i - P_v)$. All conductances are standardized to G_{vent} and G_{perf}, both constant at 1·0 units.

(1) In exercise the conductances are increased. In man and mammals, G_{vent} (i.e. $\dot{V}$) increases proportionally to $\dot{M}_{O_2}$ and $\dot{M}_{CO_2}$, by increasing both tidal volume and breathing frequency. G_{perf} also rises, due to increased cardiac output, $\dot{Q}$, brought about by increased cardiac frequency and stroke volume, but also due to increase of β_{O_2} of blood produced by lowering of venous $P_{\bar{O}_2}$ and by increase of blood haematocrit. The extent of increase of G_{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_{vent} alleviates the acidosis. In water-breathing animals, however, even a large increase in G_{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_2 and CO_2 exchange in tissues is less advanced than that in external gas exchange organs, due mainly to the experimental difficulties involved in determining P_{O_2} and P_{CO_2} in tissues and also due to problems of adequate modelling (cf. Tenney, 1974; Grunewald & Sowa, 1977).

In tissue respiration usually only O_2 is considered. The main reason for this derives from the existence of an absolute limit for tissue P_{O_2} ($P_{O_2} = 0$), whereas no such limit exists for P_{CO_2}. Moreover, all P_{CO_2} gradients are small, because of high β and high K for CO_2 (equation 8).

(A) *Models*

(1) *Krogh's cylinder*

The most widely used model for analysis of tissue O_2 supply is the Krogh cylinder (Krogh, 1919) which displays a radial and a longitudinal (arterio–venous) P_{O_2} gradient (Fig. 5A). For the total radial P_{O_2} difference (*i.e.* the difference between P_{O_2} in the axial capillary blood) P_c, and P_{O_2} at the surface of the cylinder, P_0, in any cross-sectional segment of the cylinder, the following equation is obtained assuming, (1) homogeneous distribution of O_2 consumption to tissue volume, (2) uniform diffusivity (K), and (3) no longitudinal diffusion:

$$P_c - P_0 = \frac{\dot{m}}{4K} \cdot r_0^2 [2 \ln (r_0/r_c) + (r_c/r_0)^2 - 1] \tag{9}$$

($\dot{m}$, O_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_2 conductance, d',

$$d' = \frac{4K}{r_0^2 \cdot [2 \ln (r_0/r_c) + (r_c/r_0)^2 - 1]} \tag{10}$$

one obtains:

$$P_c - P_0 = \dot{m}/d'. \tag{11}$$

The longitudinal gradient is the same in blood and in tissue at a given distance from the capillary. The corresponding total longitudinal P_{O_2} difference follows from Fick's principle:

$$P_a - P_v = \frac{\dot{m}}{\dot{q} \cdot \beta_b} \tag{12}$$

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

For the largest P_{O_2} difference, i.e. between arterial P_{O_2} and P_{O_2} at the periphery of the venous end of the cylinder, $P_{O(v)}$, one obtains by combining eqs. (11) and (12):

$$P_a - P_{O(v)} = \dot{m}\left(\frac{1}{d'} + \frac{1}{\dot{q} \cdot \beta_b}\right). \tag{13}$$

The tissue P_{O_2} in Krogh cylinder is rather varied, extending from arterial P_{O_2} to values lower than venous P_{O_2}. The volume-averaged mean P_{O_2} is usually near venous P_{O_2} (Tenney, 1974).

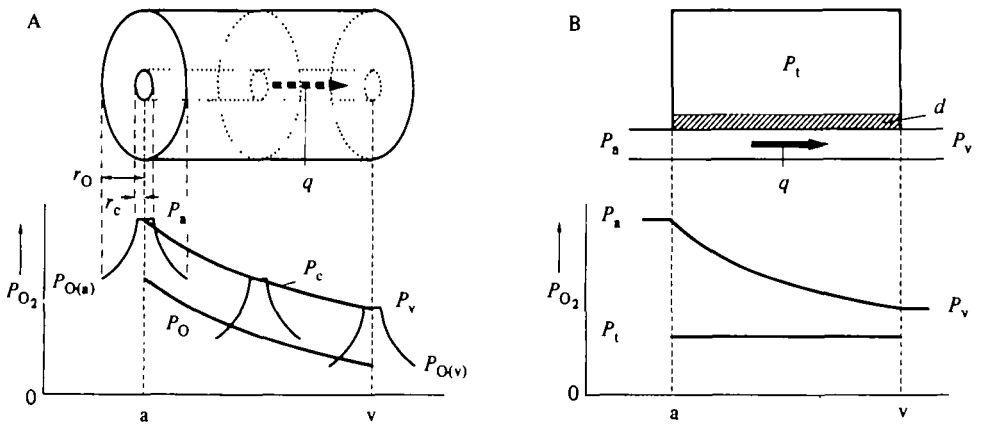

Fig. 5. Models for analysis of O_2 transfer in tissues. The lower panels show schematically O_2 partial pressure profiles in the models. (A) Krogh's cylinder with axial blood capillary. r_c, radius of capillary; r_0, radius of cylinder, $\dot{q}$, blood flow per unit tissue volume. The radial P_{O_2} profile across the tissue cylinder is shown at the arterial end (from P_a to $P_{O(a)}$) in the middle, and at the venous end (from P_v to $P_{O(v)}$). The longitudinal profile of P_{O_2} is represented for the capillary (P_c) and for the periphery of the cylinder (P_0). (B) Simplified model (total resistance to O_2 uptake in a thin layer, no P_{O_2} gradients in tissue). P_t, P_a and P_v, P_{O_2} in tissue, in arterial and in venous blood, respectively; d, diffusive conductance per unit tissue volume; $\dot{q}$, blood flow per unit tissue volume. The longitudinal P_{O_2} gradient in blood is shown (from P_a to P_v).

(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. 5 B). 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.

$$d = K.f/x \tag{14}$$

(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:

$$P_a - P_t = \frac{\dot{m}}{\dot{q}\beta_b[1 - \exp\{-d/(\dot{q}\beta_b)\}]}. \tag{15}$$

(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, β_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, β_b, has formally the same effect as increase of $\dot{q}.\beta_b$ 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_c) 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 $d/(\dot{q}.\beta_b)$ or $d'/(\dot{q}.\beta_b)$ 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

of O_2 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 O_2 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 O_2 supply in a system of parallel capillary units with unequal blood flow is reduced because it reaches critical O_2 supply conditions at lower O_2 requirement or at higher total blood flow than in a homogeneously perfused system.

For O_2 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:

$$B = dM/dP. \tag{16}$$

The capacitance is proportional to the volume, V, and to the capacitance coefficient, β:

$$B = V.\beta. \tag{17}$$

Thus the amount of O_2 liberated by lowering of O_2 partial pressure from P_1 to P_2 is

$$M = V.\beta.(P_1 - P_2) = B(P_1 - P_2) \tag{18}$$

The main cpacitances for O_2, or O_2 stores, of the body are lung gas, blood (arterial and venous), tissues (with and without myoglobin). During breath-holding, after lowering of inspired O_2 and after onset of exercise, the O_2 partial pressures in various compartments change, and thereby stored O_2 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 $\dot{M}_{O_2}$, respectively) to a new steady state value. This delayed change may be described by a characteristic time, t_0,

$$t_0 = \frac{1}{y_2 - y_1} \int_{t=0}^{t=\infty} (y_2 - y)\, dt \tag{19}$$

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

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

$$y_2 - y = (y_2 - y_1) \exp(-t/\tau). \tag{20}$$

In this case t_0 is equal to the time constant, τ, which is proportional to the half time, $t_{\frac{1}{2}}$ ($\tau = 0{\cdot}693\ t_{\frac{1}{2}}$).

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, τ is equal to the capacitance/conductance ratio

$$\tau = B/G. \tag{21}$$

This behaviour is found in the time course of CO_2 release from incubated chicken eggs upon sudden changes in environmental gas, τ 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.* 1980*b*).

(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 $\dot{M}_{O_2}$ 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:

$$M = \int_{t=0}^{t=\infty} (\dot{M}_2 - \dot{M})\, \mathrm{dt}. \tag{22}$$

($\dot{M}$, time-dependent O_2 uptake; $\dot{M}_2$, 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

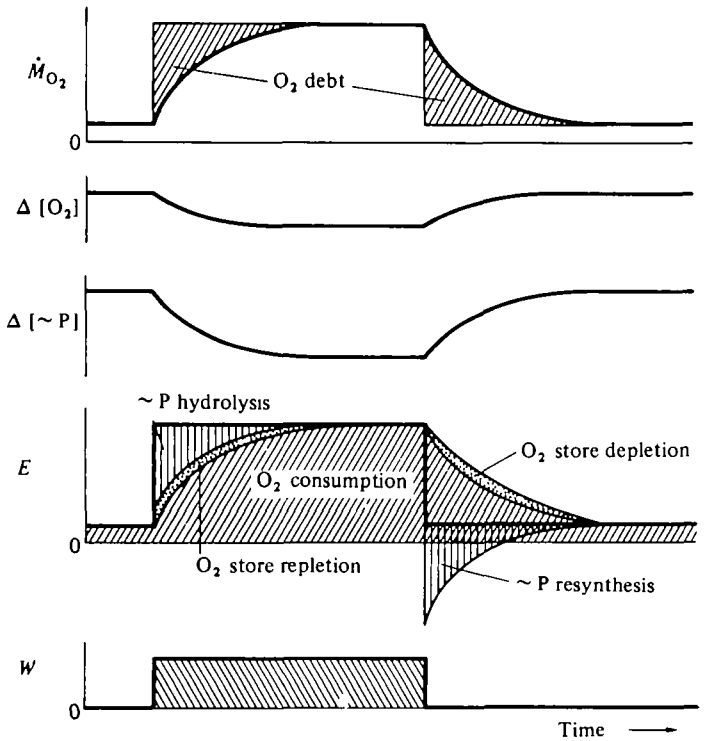

Fig. 6. Schema of the behaviour of O_2 and other variables during and after a medium exercise of constant power (in a mammal or in an isolated mammalian muscle). From top to bottom: O_2 uptake, $\dot{M}_{O_2}$; change of O_2 stores, $\Delta[O_2]$; change of high-energy phosphate concentration, $\Delta[\sim P]$; energy turnover rates, $\dot{E}$: total energy turnover rate (thick line) and its components (hatched areas); external power, $\dot{W}$. 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).

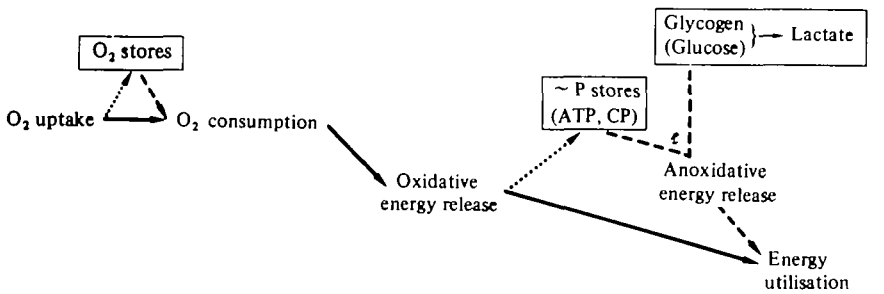

Fig. 7. Relationships between O_2 uptake, oxidative and an-oxidative energy release, and O_2 and high-energy phosphate stores, for analysis of O_2 debt. The scheme is not intended to depict the metabolic pathways: ATP is shown only in its energy storage function, not as an obligatory intermediate in energy turnover.

in vivo (cf. Piiper *et al.* 1980*a*). It has been shown that the O_2 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 O_2 debt repayment is required for resynthesis of phosphocreatine to the resting level (Piiper & Spiller, 1970).

The relationship between the kinetics of O_2 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 O_2 supply need not be instantaneous.

(*b*) The adjustments of O_2 supply are intrinsically slow, giving rise to an O_2 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 O_2 debt associated with exercise of vertebrate muscles is usually repaid during the recovery. After onset of hypoxia, however, in many lower vertebrates the O_2 uptake is reduced, and after return to normoxia there is little overshoot in O_2 uptake: this behaviour is called O_2 conformity, in contrast to O_2 regulation meaning O_2 consumption independent of O_2 supply (cf. Prosser, 1973).

In many cases the O_2 conformity appears not to be only a passive consequence of shortage of O_2 supply, but it should rather be interpreted as an adjustment to reduced O_2 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 O_2 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 O_2-debt repaid fully (or even in excess), through O_2 debt repaid partially to 'true' reduced metabolic state. Their systematic and comparative study in lower vertebrates is expected to be rewarding.

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