OXYGEN NEEDS AND VENTILATORY COUPLING

- Oxygen needs
- Pulmonary and alveolar ventilation
- Alveolar gas equation
- End-expiratory and arterial PCO₂
- Coupling between metabolism and ventilation

A very general expression of the metabolic pathways involving oxygen (aerobic metabolism) can be represented in the form of the reaction

\[ \text{O}_2 + \text{food} \rightarrow \text{water} + \text{carbon dioxide} + \text{energy} \]  (eq.1)

the stoichiometry of which depends on the type of food substrate utilized. It is important to realize that the above reaction does not mean that O₂ interacts as a substrate; in fact, O₂ never reacts directly with amino acids, lipids or sugars, nor with their simplified molecular constituents. It simply acts as a proton (and electron) acceptor at the end of the electrons transport chain, which is a complex of enzymes packaged together within the inner membrane of the mitochondria.

Indeed, the very same properties that make oxygen an ideal electron acceptor would cause major cellular damage if oxygen was left free to react within the cytosol. Oxygen is a major toxic agent, and most animals, including man, would seriously suffer if exposed to high oxygen concentrations for protracted periods of time, and die within a few days if forced to breathe 100% O₂ [Fig.1], with dyspnea and hypoxemia resulting from pulmonary edema. If pure O₂ was administered at higher pressures, death could be extremely rapid, with convulsions due to the
toxic effect of O₂ on the nervous system.

![Graph showing survival of rats of different age exposed to >95% O₂ breathing for 3 days.](Image)

**Fig.1. Survival of rats of different age, when exposed to >95% O₂ breathing for 3 days.** (Modified from Frank, Fed.Proceed. 44:2328-2334, 1985)

Most cells are equipped with a variety of mechanisms to deal with the oxidative effects produced by internal 'leaks' of oxygen and its radicals; some of these mechanisms are represented by a battery of enzymes (scavengers) designed to immediately neutralize the oxidative effects of the free radicals, whereas other mechanisms are designed to continuously repair the unavoidable structural damages. Superoxide dismutases (SODs) catalyze superoxide (O₂⁻) into hydrogen peroxide (H₂O₂); H₂O₂ is potentially very toxic, especially because it can be reduced in the highly reactive and damaging hydroxyl radical OH⁻. Normally, this transformation is avoided by cellular catalases and peroxidases, which dismute and reduce H₂O₂ to H₂O. Dismutases, catalases and peroxidases are probably the main cellular players in the defensive team against O₂ free radicals. Many others are known, like α-tocopherol and carotenoids (vitamin A), ascorbate (vitamin C), etc.

Hence, one could look at the interaction of O₂ with the living matter as a form of fine balance between the advantages coming from its use in the process of aerobic energy production (oxidative phosphorylation) and the risks involved with its handling at the cellular level (oxygen toxicity).
In steady state conditions, the question of how much oxygen we need to consume (oxygen consumption, $V_{O_2}$), either to rest, to exercise, or simply to survive (basal oxygen consumption) can be easily answered by direct measurements (e.g. a modified spirometer) or indirect estimates (indirect calorimetry). In steady state, which is the situation here assumed for the sake of simplicity, the uptake of $O_2$ at the pulmonary level corresponds to $V_{O_2}$, i.e. pulmonary uptake = body (tissue) consumption. Equally, the pulmonary elimination of $CO_2$ corresponds to the body production of $CO_2$ ($V_{CO_2}$). In dynamic conditions, however, there may be major differences between pulmonary $O_2$ uptake or $CO_2$ elimination and, respectively, $V_{O_2}$ or $V_{CO_2}$, because of the body stores of $O_2$ (rather small) and of $CO_2$ (very large).

In the adult man, basal $V_{O_2}$ is about 250-300 ml/min, or 3-4 ml/kg/min, and it can increase more than 20 fold during strenuous exercise, until its maximal value, $V_{O_2}$ max [Fig.2]. $V_{CO_2}$ is between 70 and 100% of $V_{O_2}$. Values of $V_{O_2}$ and $V_{O_2}$ max differ
Fig.2. Oxygen consumption (O₂) as function of time during exercise of progressively greater intensity (1<2<3<...), all beginning from rest. Exercise 6 is "supra-maximal", i.e. it does not raise VO₂ above what attained with exercise level 5. In the right panel, the VO₂s attained at the various exercise levels are plotted against the intensity of the exercise. The plateau in the Power-VO₂ function indicates VO₂max.

between genders, and with age [Fig.3]; to some extent, these difference persist even after normalization by body weight. Major differences in VO₂/kg occur among species, larger mammals needing less O₂, per unit weight, than smaller species do.

![Graph showing VO₂max vs age in males and females.](image)

**Fig.3.** VO₂max vs age in males and females. After puberty, females have lower values than males, and in both genders VO₂max decreases with age. Obviously, for an aerobic exercise, a high VO₂max is crucial. However, what would you consider more important, VO₂max in absolute values, or VO₂max/kg?

Although a small component of O₂ can be used in the cytosol by oxidases and oxygenases, almost all VO₂ is for the purpose of producing chemical energy and heat. The former is eventually used to drive enzymatic reactions which are energetically unfavourable, to maintain electrochemical gradients, or converted into other forms of energy, including external work and heat. In invertebrates and lower vertebrates (fish, amphibia and reptiles) ambient temperature (Ta) is an important determinant of the speed of enzymatic reaction, and therefore of VO₂. As Ta increases VO₂ increases, approximately doubling for every 10°C [Fig.4]. Indeed, all these animals are poikilotherms, meaning that their body temperature (Tb) is not constant but varies with
Fig. 4. Changes in the speed of enzymatic reaction (and therefore in VO$_2$, in a steady state aerobic condition) with changes in temperature ($Q_{10}$ effect). The dashed vertical lines indicate the most common range of body temperature in adult mammals; however, in many cases (e.g. hibernation, torpor, or hypoxia especially in newborns) body temperature can decrease to very low values.
the environment, and their VO₂ is Ta-dependent. In homeotherms (birds and mammals), on the other hand, Tb tends to be controlled by mechanisms of heat production (thermogenesis) and heat dissipation. Hence, some of the resting VO₂ is for the production of thermal energy, in an effort to maintain Tb within narrow limits, irrespective of changes in Ta. In most mammals Tb is maintained around 36-37°C, whereas in birds is around 38-39°C. It follows, therefore, that in homeotherms, differently from poikilotherms, VO₂ increases not only with an increase in Ta, but also when Ta decreases [Fig.5].

![Diagram](image)

**Fig.5.** As ambient temperature (Ta) decreases below thermoneutrality, oxygen consumption (VO₂) increases, maintaining body temperature (Tb). When thermogenesis does not suffice, Tb begins to fall (critical Ta). The ability to maintain a thermoneutral range is mostly due to an increase in heat dissipation. Eventually, with further increases in Ta, heat-loss mechanisms will not prevent a rise in Tb, which will also lead to a rise in VO₂.

Over some range of Ta, VO₂ is actually steady at a minimum level, since Tb is controlled by altering the magnitude of heat dissipation. This range is called thermoneutrality, physiologically defined as the range in Ta with maintenance of Tb with minimal normoxic VO₂. The specification 'normoxic' is important, because hypoxia can decrease VO₂. Above thermoneutrality VO₂ increases, partly because of the Q₁₀, partly because of the cost of heat dissipating mechanisms. Below thermoneutrality, VO₂ increases because of thermogenesis. The latter includes behavioural thermogenesis (e.g. changes in location, postural changes), shivering (muscle contraction for the purpose of generating heat) and non-shivering thermogenesis (heat produced by specialised
organs, namely the brown adipose tissue). The relative contribution of these thermogenic
mechanisms, and their threshold of activation, vary among species and with age. For example, in
the neonatal period shivering is rare, whereas brown fat thermogenesis represents the major
mechanism of heat production. At very low Ta, VO₂ begins to fall, partly because of the Q₁₀
effect, partly because of the inhibitory effect of hypothermia on thermogenic mechanisms.

Hence, in very cold conditions, thermogenic mechanisms do not suffice, Tb begins to falls and
its drop further reduces VO₂, leading to a vicious cycle of progressive hypothermia.
Thermoneutrality is an important physiological concept, useful also for the interpretation of the
interaction between heat producing and heat dissipating mechanisms. However, it needs to be
emphasized that the large majority of homeotherms, even during the early phases of postnatal
development, do not live in thermoneutral conditions; their preferred Ta is at the lower end of, or
frequently slightly below, thermoneutrality.

**PULMONARY AND ALVEOLAR VENTILATION**

Because in most mammals, including newborns the skin represents an irrelevant route for gas
exchange, gaseous metabolism, i.e. the exchange of oxygen and carbon dioxide with the
environment, must depend on pulmonary ventilation. Hence,

\[ \text{VO}_2 = \text{VE} \cdot ([\text{O}_2]_I - [\text{O}_2]_E) \tag{eq.2} \]

and

\[ \text{VCO}_2 = \text{VE} \cdot ([\text{CO}_2]_I - [\text{CO}_2]_E) \tag{eq.3} \]

where I and E represent, respectively, the mean inspired and expired concentrations of O₂ and
CO₂, and inspired and expired ventilation are assumed to be the same *.

[*Strictly, this would be true only if the respiratory exchange ratio (VCO₂/VO₂) was equal to
unity; more often it is between 0.7 and 1]*

Hence, changes in VO₂ can be accommodated by changing the extraction of O₂ from the inspired
air, i.e. by widening the I-E [O₂] difference, or by increasing VE, in any combination. In addition,
a particular level of VE can be achieved by various combinations of breathing frequency (f) and
tidal volume (VT).

The possibility of varying f and VT, i.e. of changing breathing pattern, for any particular level
of VE, has profound implications on the ventilation of the alveolar regions (VA), and is therefore
crucial for gas exchange and its proper matching to VO₂. In fact, VT is the sum of the alveolar
volume (VA) and the dead space (VD), and the latter can be taken almost as a constant, since its
volume largely reflects the structural characteristics of the airways*.

[*VD increases during inspiration, especially during deep breathing, lowering airways resistance.
However, its volume changes are small compared to the increase in VT]*

The following example, from a human subject with VD=200 ml, illustrates this point:

\[ \text{VE} = \frac{\text{VT}}{\text{f}}, \text{ and } \frac{\text{VA}}{\text{f}} = \frac{\text{VA}}{\text{f}} \]

(br./min) (ml/min) (ml) (breaths/min) (ml)
**case a.**

\[
4000 = 500 \cdot 8 \quad (500-200) \cdot 8 = 2400
\]

**case b.**

\[
4000 = 250 \cdot 16 \quad (250-200) \cdot 16 = 800
\]

Hence, for the same VE of 4000 ml/min, the rapid and shallow pattern (case b) reduces VA from 2400 ml/min of case a to only 800 ml/min. Indeed, for any given VE, the deeper the breathing pattern the more efficient it becomes from the viewpoint of alveolar convection, since VD reduces its burden on VT. Eventually, energetic constraints pose a limit to the gas exchange advantage of the deep and slow breathing pattern.

**ALVEOLAR GAS EQUATIONS**

From the above, it is apparent that VE is a parameter of importance in considering various aspects of the energetics and of the regulation of the breathing act; however, from the viewpoint of gas exchange and of accommodating the metabolic needs of the organism VA, not VE, is the parameter of major functional interest. Hence, if we are concerned about the coupling between pulmonary convective mechanisms and metabolic needs, eq 1. should be more properly expressed with respect to the alveolar level (A), in the form of

\[
VO_2 = VA \cdot [O_2]_{insp} - [O_2]_A \quad \text{(eq.4)}
\]

and

\[
VCO_2 = VA \cdot [CO_2]_A - [CO_2]_{insp} \quad \text{(eq.5)}
\]

Because the partial pressure P of a gas within a gas mixture equals the product of its fractional concentration and the total dry pressure, equations 4 and 5 can be expressed with reference to the partial pressure of O₂ (P_{O_2}) and CO₂ (P_{CO_2}), rather than their concentrations:

\[
PAO_2 = P_{O_2} - \left(\frac{VO_2}{VA}\right) \cdot Pb \quad \text{(eq.6)}
\]

and

\[
PACO_2 = P_{CO_2} + \left(\frac{VCO_2}{VA}\right) \cdot Pb \quad \text{(eq.7)}
\]

Pb representing the dry barometric pressure, and neglecting the small difference between inspired and expired ventilation introduced by a respiratory exchange ratio less than unity.

Fig.6 provides the graphical representation of the alveolar gas equations for O₂ and CO₂ (eq.6 and 7), during air breathing at
Fig. 6. Graphical representation of the alveolar gas equation for O₂ (top) and CO₂ (bottom), during air breathing at sea level, and at arbitrarily chosen metabolic rates (VO₂ and VCO₂) of 100 ml/min (continuous line) and 200 ml/min (dashed line). Inspired O₂ 21%, inspired CO₂ 0%, barometric pressure 760 mm Hg.

sea-level, for two arbitrarily chosen levels of metabolic rate, m (continuous lines) and 2m (dashed lines). In examining these hyperbolic relations, several aspects need to be emphasized.
As VA increases, PAO₂ rises toward the inspired value, and PACO₂ decreases also approaching the inspired value which, in the usual case of breathing air, is almost zero. Doubling VA halves the PACO₂ value (eq.6); therefore, the absolute drop in PACO₂ progressively decreases as VA increases. For example, for an increase in VA from 3 to 6 l/min, PACO₂ drops from 44 to 22 mm Hg, i.e. by 22 mm Hg. On the other hand, the same increase in VA from 12 to 15 l/min will reduce PACO₂ by less than 3 mm Hg.

It is also worth noticing that even a large change in VA when VA is already at high levels has little consequences on PAO₂, whereas a small further drop when VA is already low can cause an important fall in PAO₂.

The shape and position of the metabolic hyperbola depend on the metabolic level and the inspired concentration of the gases. For example, for CO₂ [Fig.6, bottom panel], an increase in metabolic rate, or re-breathing (i.e. breathing air with CO₂ in it) will displace the curve upwards. Therefore, the same PACO₂ can occur at many different levels of VCO₂ and VA combinations. It follows not only that there is no unique relationship between VA and PACO₂, but also that an increase in VA does not necessarily imply a decrease in PACO₂. It is important to distinguish between an increase in VA relative to its 'normal' reference value, and an increase in VA relative to the corresponding metabolic level. The former is called hyperpnea, the latter hyperventilation.

Hence, hyperventilation can be defined as any situation that results in a drop in PACO₂, irrespective of the absolute level of VE and VA (see eq.7). In other words, hyperventilation can occur even with a decrease in the absolute level of VA (hypopnea) if metabolism decreased even more than VA did; this seemingly unusual combination of hypopnea and hyperventilation is not a rare event during acute hypoxia in the neonatal period. Conversely, constancy in PACO₂ (isocapnia) indicates that the level of VA is maintaining its proportionality with the metabolic demands (VA/VCO₂ = constant); in such a case, the subject is normo-ventilating, again, irrespective of the absolute level of VE or VA.

**END-EXPIRATORY PCO₂ AND ARTERIAL PCO₂**

Let’s consider the signal of a rapid CO₂ analyser, sampling the expired air at the mouth. At first, the CO₂ concentration (and PCO₂) would be close to nil, since the first air expired originates from the dead space, which is filled by the inspired gas (about 0.03% CO₂). Only after the whole VD has been expired, PCO₂ will increase, to a value that could approach the alveolar value [Fig.7].
Fig. 7. Time profile of alveolar and mouth PCO$_2$ in expiration and inspiration during resting breathing. Mouth PCO$_2$ follows closely the alveolar value toward the end of expiration (end-tidal PCO$_2$)

The time average of mouth PCO$_2$ is the mean expiratory value, whereas the end-expiratory PCO$_2$ (also called end-tidal PCO$_2$) corresponds to PACO$_2$. As indicated in the figure, PACO$_2$ continues to rise until fresh inspired air reaches the alveoli, hence it rises for the whole expiratory phase and for the first part of inspiration (VD washout). The end-tidal PCO$_2$ is a convenient measurement because the alveolar value, in an healthy individual, is very close to the arterial value; in fact, for most practical purposes, PACO$_2$ = PaCO$_2$. Only in the presence of large shunts or major ventilation-perfusion inequalities can PaCO$_2$ be appreciably higher than PACO$_2$.

COUPLING BETWEEN METABOLISM AND VENTILATION

Some of the most studied conditions of changes in metabolic level are those during muscle exercise and increased thermogenesis. In several species, including man, VE increases in proportion with VO$_2$ during modest and moderate exercise, and only at the most severe levels of exercise VE increases disproportionately more than VO$_2$ [Fig. 8, left]. The latter reflects the additional stimulus on ventilation by the lactic acidosis present at the highest aerobic working levels.

Fig. 8. Examples of the changes in ventilation (VE) when oxygen consumption (VO$_2$) increases because of muscle exercise (left) or cold-induced thermogenesis (right). The constancy in PaCO$_2$ indicates that there is no hyperventilation, i.e. the hyperpnea is proportional to the increased metabolic requirements.

Cold induced thermogenesis [Fig. 8, right], circadian oscillations in metabolic rate, pharmacological stimulants of VO$_2$, are other examples of the tight coupling between VE and VO$_2$. In all these cases, in fact, even large changes in VO$_2$ can occur with no or minimal changes in PaCO$_2$. 