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Abstract. In this short review, the frame of current understandings concerning what determines the upper limit of oxygen flow from the ambient air to the muscular mitochondria during maximal dynamic exercise in humans (i.e.,  $\dot{V}O_2max$ ), was summarized mainly from its modeling perspective. Several models and experimental evidences which appeared repeatedly in the recent debates regarding the factors limiting  $\dot{V}O_2max$ , were adopted and criticized. In conclusion,  $\dot{V}O_2max$  is determined in particular by the integrated interaction between the diffusive and convective factors both to lung  $O_2$ -loading and muscular  $O_2$ -unloading in the pathway for  $O_2$  flow, although all experimental observations cannot be satisfactorily explained at the present time. (Appl Human Sci, 14(6): 259–270, 1995)

Keywords: human, maximal oxygen uptake, diffusive/ convective interaction, muscular  $O_2$ -unloading, Bohr effect

# Introduction

The maximal oxygen uptake in lung (exactly, the maximal oxygen uptake 'rate';  $\dot{V}O_2max$ ) has been commonly known as the precise indicator which can evaluate the functional capacity (the regulation ability) of the overall system for oxygen ( $O_2$ ) transfer from ambient air to mitochondria in the working muscle. A physiological definition of  $\dot{V}O_2max$  is expressed as the Fick's equation,

$$\dot{V}O_2 \max = \dot{Q}\max \cdot (CaO_2 - C\bar{v}O_2)$$
  
= "O<sub>2</sub>-delivery" -  $\dot{Q}\max \cdot C\bar{v}O_2$ . [Eq.1]

A great number of investigations had been devoted to clarify what factor(s) of the three determinants in Eq. 1 limits the  $\dot{V}O_2max$  in the recent half century. Consequently, as a common and classical concept, the  $\dot{V}O_2max$  had mostly been considered to be limited by the Qmax and/or the O<sub>2</sub>-delivery (e.g., see Cerretelli and di-Prampero, 1987; Ekblom, 1986). This concept was derived mainly from the facts which showed the relevant associations between the change of  $\dot{V}O_2$ max under several experimental manipulations to alter the CaO<sub>2</sub> or O<sub>2</sub>-delivery such as the acute and chronic hyperoxia/ hypoxia (increasing/decreasing PIO<sub>2</sub>), the blood infusion/withdrawal, the CO inhalation, the acute anemia, and so on, though some findings have not always been confirmed.

The other prominent concept was derived from the field of comparative physiology (e.g., see Dejours, 1981). The hypothesis called "symmorphosis", was defined as "a state of structural design commensurate to functional needs resulting from regulated morphogeneses" by Taylor, Weibel and their associates (Weibel and Taylor, 1981). In their concept, there is no weak linkage of  $O_2$  transport and utilization, because each site which included the whole  $O_2$  transport system is tightly matched to every other site functionally. For example, the physical training must increase the functional ability in all sites in proportion to the increase of  $\dot{V}O_2$ max.

In 1980s, several groups have started to challenge such classical concepts using excellent both experimental and modeling strategies. Consequently, the limiting factors to the  $\dot{V}O_2$ max have been debated actively from several different viewpoints. Therefore, in this short review, we overview the frame of current and up-date understandings concerning what limits and determines the  $\dot{V}O_2$ max, mainly from its modeling perspective, especially focussing on the peripheral site.

It has to be acknowledged that, at present time, there are several divergent positions on this topic with lively debates continuously in literatures and at scientific meetings (e.g., see Barkley, 1995; Piiper, 1990). Therefore, at the outset, it should be stated that we take a position, at least, mainly from the view points of

respiratory and circulatory physiology, not biochemistry.

# The definition of $\dot{V}O_2$ max

Before the argument, we should define the  $\dot{V}O_2$ max which we use in this review, because some controversies which cause mainly between the physiologist and the biochemist have been dependent on *the* definition (Connett and Honig, 1989). The physiologist usually considers the exercise engaging the large mass of the muscles, in which the  $O_2$  supply to the active muscle is limited by the limited pumping capacity of the heart. On the other hand, the biochemist sometimes argues the result from the isolated muscle or the small muscle which has a virtually unlimited  $O_2$  supply (i.e., the unlimited pumping capacity).

For example, imagine that the highest  $\dot{V}O_2$  was measured, not  $\dot{V}O_2$ max, from an electrically stimulated animal muscle or limb under the artificial control of blood flow externally. It is, of course, one of the elegant tools in the physiological investigations. However, a so-called ' $\dot{V}O_2$ max' has to include the functional criteria of the maximum on the Fick's equation (Eq.1), that is, the maximal cardiac output (Qmax) and the maximal arterio-venous  $O_2$  difference (a-vO<sub>2</sub>diff.). This means that Qmax is constrained by the limited pump capacity of the heart and the control of the autonomic nervous system. The situation of this example is precisely limited by those artificially set by the investigator rather than by the animal.

Therefore, it should be reminded the laboratory in where the  $VO_2$ max measurement is usually performed. That is, the healthy human subject does exercise intactly on the cycle ergometer or treadmill with a progressive increase of the work rate until exhaustion under the normal environmental conditions (i.e., the sea-level, neutral ambient air temperature and humidity, etc). In other words, such exercise mode corresponds to be 'systemic' and 'dynamic' with a large muscle mass in vivo (in situ). During the exercise, the pulmonary gas exchange parameters are measured simultaneously. At very high work rates where, despite increases in power output by the subject, the measured pulmonary  $\dot{V}O_2$  fails to increase further. This plateau or maximal value of  $\dot{V}O_2$  is termed ' $\dot{V}O_2$ max' (Fig.1). However, keep it on your mind that the observations in several animal species exercising intactly or in isolated perfused muscle preparations give a deep insight on the fundamental understandings to the factors limiting the VO<sub>2</sub>max in humans.

#### The pathway of O<sub>2</sub> flow

There are several functional and structural barriers



Fig. 1 Typical example of the VO<sub>2</sub>max measurement in cycle ergometer exercise with different ramp slopes in a single subject studied in our laboratory (unpublished data).

along the route of the pathway of serial  $O_2$  flow ( $O_2$  transfer) from the ambient air to the mitochondrion in the working muscle. Namely,

- 1) convective transfer from the atmosphere to the alveolar gas by the pulmonary ventilation,
- 2) diffusive transfer across the alveolar membrane to the arterial blood,
- 3) convective (perfusive) transfer to the capillaries in the working muscles through the blood circulation which is pumped by the heart, and
- diffusive transfer to the mitochondria across the capillary, cellular, and mitochondrial membranes.

Finally, the supplied  $O_2$  to the mitochondria contributes to the ATP turnover for the muscular contraction within the limit of its turnover rate. These limiting steps are represented in Fig.2 schematically. The equation which shows a functional factor of each step on the  $O_2$ -pathway was also described in Fig.2. As structural factors that are supposed to impose the potential limitation on O<sub>2</sub>-pathway, total alveolar surface, total capillary surface, capillary blood volume and thickness of plasma tissue in the lung O2-loading, hemoglobin concentration and stroke volume in the circulatory O2-transfer, total capillary length and capillary blood volume in the muscular O2-unloading, and volume of mitochondria and surface of inner mitochondrial membrane in the muscular O<sub>2</sub>-utilization should be taken into account (Taylor et al., 1987).

The central and fundamental question in this review is how these steps determine the upper limit of the  $O_2$  flow (i.e.,  $\dot{V}O_2max$ ) across the serial barriers. In the

following sections, therefore, main potential sites of the barriers limiting the maximal  $O_2$  flow, especially the muscular  $O_2$ -unloading site are discussed.

### $O_2$ conductance theory

Based on several physiological steps on the pathway for  $O_2$  flow from ambient air to mitochondrion as described in Section 3, the causes which are supposed to limit the  $\dot{V}O_2$ max have been generally postulated in the following:

- 1) due to the limitation in the pulmonary function which maintains the adequate  $PaO_2$  by the alveolar ventilation,
- 2) due to the limitation of the central circulatory function which maintains the adequate O<sub>2</sub>-delivery by the pumping capacity of the heart,
- 3) due to the limitation of the peripheral circulatory function which maintains the necessary blood flow to the active muscle region by the cardiovascular controllability, and
- 4) due to the limitation of the muscular metabolic function which maintains the necessary ATP turnover rate by the oxidative capacity of the mitochondrial enzymes.

Among these factors, the diffusive function both in alveolar and muscular cell membranes has not been



Fig. 2 Summarized representation of functional factors that impose potential limitation on  $O_2$ -transfer from the ambient air to muscular mitochondria.  $\dot{V}O_2$ (mit) and  $V_{mit}$  are 'assumed'  $\dot{V}O_2$  per mitochondrion and total volume of mitochondria.

adopted for a long time. One of the reasons was probably ascribed to the misunderstanding of the 'serial'  $O_2$ -conductance theory. As already stated in Section 3, on the  $O_2$ -pathway, the  $PO_2$  from the ambient air to mitochondrial cristae decreases progressively as a stepwise manner by each potential barrier, namely as if a 'cascade' system (Fig.3).

In the serial cascade system, the decline of each potential site is determined by each conductance of the barrier (see Fig.4). A conductance (G) is the reciprocal of the corresponding resistance (R). It is possible to consider in terms of an electrical analogue for any conductance. The electrical analogue is governed by Ohm's law, with an electrical voltage (*e*) across an individual link in the system being proportional to the product of the flux (*I*) and resistance (i.e.,  $e=I \cdot R$ , or e=I/G). Therefore, the O<sub>2</sub> pathway can be treated as the same as a serial cascade of the resistances, with each resistance (R\*) overcome by a specific PO<sub>2</sub> gradient ( $\Delta P_*$ ). Namely, O<sub>2</sub> flux ( $\dot{V}O_2$ ) is,

$$\dot{V}O_2 = \Delta P_*/R_* = \Delta P_* \cdot G_* = \Delta P_T/R_T$$
 [Eq.2]

where  $\Delta P_T$  and  $R_T$  mean the overall pressure gradient from PIO<sub>2</sub> to PmO<sub>2</sub> and the overall resistance to O<sub>2</sub> flow.

diPrampero and Ferretti (1990) constructed the "multifactorial" model derived from the following  $O_2$  conductance equation to evaluate each resistance potential as a limiting factor (Fig.4a).

$$\begin{split} \bar{V}O_2max &= (PIO_2 - PAO_2)/R_v = (PAO_2 - PaO_2)/R_1 \\ &= (PaO_2 - P\bar{v}O_2)/R_q = (P\bar{v}O_2 - PmO_2)/R_m \\ &= \Delta P_T/R_T \end{split}$$

where the overall resistance from ambient air to mitochondrion ( $R_T$ ) is portioned in the following steps depending on alveolar ventilatory resistance ( $R_v$ ), lung  $O_2$ loading resistance ( $R_1$ ), circulatory convective resistance ( $R_q$ ), and peripheral  $O_2$ -unloading resistance ( $R_m$ ). The relative contribution of the potential of each resistance limiting the  $\dot{V}O_2$ max is expressed as the fraction ( $F_*$ ) of the corresponding pressure decline to the overall pressure gradient,

$$\mathbf{F}_* = \mathbf{R}_* / \mathbf{R}_{\mathrm{T}} = \Delta \mathbf{P}_* / \Delta \mathbf{P}_{\mathrm{T}}.$$
 [Eq.4]

If each gradient of  $(PAO_2 - PaO_2)$ , and  $(P\bar{v}O_2 - PmO_2)$  is adopted to evaluate the resistance both in pulmonary and muscular cell membrane barriers, of course, both potentials to the overall resistance are relatively small compared with the convective resistance (i.e., the gradient of  $(PaO_2 - P\bar{v}O_2)$ ) in the usual environmental situations at sea-level (for typical example:  $F_1 = (120 - 95)/$ 150 = 0.17,  $F_q = (95 - 20)/150 = 0.50$ ,  $F_m = (20 - 0)/150 = 0.13$ where pressure is expressed as torr). This result agreed quite well with the classical concept in which the  $\dot{V}O_2$ max was mainly limited by the convective factor, name-



Fig. 3 Schematic illustration of a progressive decline of PO<sub>2</sub> on the O<sub>2</sub>-cascade.

ly  $F_q$  (diPrampero and Ferretti, 1990).

However, it should be noticed that both  $PaO_2$  and  $P\overline{v}O_2$  (precisely,  $PvO_2$ ) which are the consequences of the  $O_2$ -loading through alveolar gas exchanger and  $O_2$ -unloading through muscular gas exchanger, are determined by not only convection but also diffusion, that is, by the interaction of both diffusive and convective conductances, not solely by either of them.

Otis (1987) also applied the same strategy to analyze the relative contribution of each potential site to the  $O_2$ flow limitation (Fig.4b). As the convective conductance, the gradient of mean pulmonary and muscular capillary  $PO_2$  (i.e.,  $P\overline{pc}O_2 - P\overline{mc}O_2$ ) was used instead of  $(PaO_2 - P\overline{mc}O_2)$  $P\bar{v}O_2$ ). Although the circulatory convective potential might be reflected to the gradient from  $P\overline{pc}O_2$  to  $P\overline{mc}O_2$ qualitatively, either  $P\overline{pc}O_2$  or  $P\overline{mc}O_2$  is also determined by both convective and diffusive interaction. Recently, Shephard (1992) simplified this theory as serial two respiratory and cardiovascular conductances to the overall conductance (Fig.4c), because the O<sub>2</sub> driving pressures change continually on moving along the capillaries both in the lung and muscle. This conservative analysis may be reasonable and appropriate, however, it can evaluate only the relative contribution by just two components potential, i.e., the pulmonary convective (=  $F_v$ ) and the remaining factor (= 1- $F_v$ ).

In order to understand the interaction of diffusive and convective conductances of gas exchanger site in both lung and muscle, a simple example is given. Imagine PaO<sub>2</sub> when pulmonary blood flow is abnormally high to the normal diffusion capacity, or diffusing capacity is abnormally low to the adequate blood flow level at a specific required pulmonary oxygen uptake. You can easily notice the consequence that equilibration is achieved incompletely, in other words, very wide alveolar-arterial  $PO_2$  difference appears just as the phenomenon of  $\dot{V}_A/\dot{Q}$  mismatching. Namely, it should be taken into consideration that the diffusive/perfusive interaction precisely affects  $PaO_2$  and  $PvO_2$  as the outlet of gas exchanger. The quantitative analysis of such interaction in the lung is firstly performed by Piiper's group as shown in the next section. We point out that the ordinal O<sub>2</sub>-conductance theory, except that by Shepherd, is not of great value to quantify the magnitude of each site potential limiting the VO₂max.

# The diffusive/convective interaction in lung O<sub>2</sub>-loading

Under the assumptions that the lung is functionally an 'ideal' gas exchanger with homogeneous gas/blood barrier and steady state blood flow, and that blood  $O_2$ dissociation curve ( $O_2$ -DC) is linear, Piiper and Scheid (1981) derived the pulmonary capillary PO<sub>2</sub> at any point x (PpcO<sub>2</sub>(x)) along the 'assumed' uniform capillary tube which has the total length of the alveoli-capillary contact ( $x_0$ ):

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Fig. 4 Diagram of gas transfer system for  $O_2$  considered as (a) 4 conductances, (b) alternative 4 conductances, and (c) 2 conductances proposed by diPrampero and Ferretti (1990), Otis (1987), and Shephard (1992), respectively. The  $O_2$  flows along the system from ambient air (left) to mitochondria (right) at rate  $\dot{M}$ , and each conductance (G) is defined as  $G=\dot{M}/\Delta P$ .

$$\begin{split} & [\mathrm{PAO}_2 - \mathrm{PpcO}_2(\mathbf{x})] / [\mathrm{PAO}_2 - \mathrm{P}\bar{\mathbf{v}}\mathrm{O}_2] \\ & = & \exp[-\{\mathrm{D}_{\mathbf{p}} / (\dot{\mathbf{Q}}_{\mathbf{p}} \cdot \boldsymbol{\beta})\} \cdot (\mathbf{x} / \mathbf{x}_0)], \end{split} \tag{Eq.5}$$

where  $\beta$  is the capacitance coefficient or the conversion coefficient between content (C) and pressure (P) on O<sub>2</sub>-DC. The Eq.5 predicts the pulmonary capillary end (i.e., PpcO<sub>2</sub>(x<sub>0</sub>)=PaO<sub>2</sub> at x=x<sub>0</sub>),

$$\begin{split} & [\operatorname{PaO}_2 - \operatorname{P}\bar{v}O_2] / [\operatorname{PAO}_2 - \operatorname{P}\bar{v}O_2] \\ &= 1 - \exp[-\{\operatorname{D}_p / (\dot{\mathbf{Q}}_p \cdot \boldsymbol{\beta})\}]. \end{split} \tag{Eq.6}$$

This equation shows "the completeness of equilibration achieved" which is exactly determined by the ratio:  $D_{p}/(\dot{Q}_{p} \cdot \beta)$  (Fig.5a). As seen in Fig.5a, the PaO<sub>2</sub> resulting from the O<sub>2</sub> equilibrium between alveolar gas and blood is recharged in proportion to the increase of  $D_p/(\dot{Q}_p \cdot \beta)$ ratio which means  $D_p$  is relatively larger to  $\dot{Q}_p$  or  $\dot{Q}_p$  is relatively smaller to  $D_p$ . The maximal  $O_2$  flow through the gas exchanger in the lung under the normoxic condition is determined by the interaction of both diffusive  $(D_p)$  and perfusive  $(\dot{Q}_p)$  factors, but relatively by the perfusion limited, because the ratio of  $D_p/(\dot{Q}_p \cdot \beta)$  is approximately between 1 to 3. On the contrary, under the hypoxic condition, as the ratio of  $D_p/(\dot{Q}_p \cdot \beta)$  becomes lower to that of normoxia, that is mainly the diffusion limited. This modeling clearly shows PaO<sub>2</sub> which can affect the CaO<sub>2</sub> and O<sub>2</sub>-delivery, is precisely determined both by the convective and diffusive interaction in the lung gas exchange.

It should be, however, noticed to the limitations of the model assumptions, which may not be realized in real lung: 1) the constancy of  $\beta$ , i.e., linear blood O<sub>2</sub>-DC, especially in normoxic condition, not seriously in hypoxia, 2) steady state, i.e., constancy of all variables in time, 3) nature of  $D_{\rm p}$  as a flat membrane of homogeneous composition, and 4) functional homogeneity, i.e., uniform  $\dot{V}_{\rm A}/\dot{Q}_{\rm p}$  (see Piiper and Scheid (1981) for the details).

# The diffusive/convective interaction in muscular O<sub>2</sub>-unloading

a) The integrated model of perfusion/convection by Wagner's group

Muscle  $O_2$  uptake ( $\dot{V}_T O_2$ ), not the same as pulmonary  $\dot{V}O_2$ , is determined both by mass flow of  $O_2$  and its subsequent diffusion into the muscle cells. Fick's equation and Law of diffusion are both representative of this process. Namely, the same as in Eq.1, the convective flux is expressed as:

$$V_{T}O_{2} = Q_{T} \cdot (CaO_{2} - CvO_{2})$$
  
=  $\dot{Q}_{T} \cdot [Hb] \cdot \alpha \cdot (SaO_{2} - SvO_{2})$   
=  $\dot{Q}_{T} \cdot [Hb] \cdot \alpha \cdot (\lambda a \cdot PaO_{2} - \lambda v \cdot PvO_{2})$   
= "O<sub>2</sub> - delivery" -  $\dot{Q}_{T} \cdot [Hb] \cdot \alpha \cdot \lambda v \cdot PvO_{2}$ , [Eq.7]

and the diffusive flux as:  $\dot{V}_T O_2 = D_T \cdot (P\bar{m}\bar{c}O_2 - PmO_2) = D_T \cdot (k \cdot PvO_2 - PmO_2),$ 

where [Hb] is haemoglobin concentration,  $\alpha$  is the O<sub>2</sub>-carrying capacity of Hb, SaO<sub>2</sub> and SvO<sub>2</sub> are the arterial and muscular end-capillary (v) Hb saturations, k is a proportionality factor of PvO<sub>2</sub>  $\propto$  PmcO<sub>2</sub>, and  $\lambda$ a and  $\lambda$ v are the conversion coefficients between saturation (S) and pressure (P) on the O<sub>2</sub>-DC affected by pH, temperature, 2-3-DPG etc.

As mitochondrial PO<sub>2</sub> (PmO<sub>2</sub>) can fall to near zero



Fig. 5 The effect of diffusive/convective interaction (for different values of  $D/(\dot{Q} \cdot \beta)$  ratio) on (a)  $O_2$ -loading in the lung and (b)  $O_2$ -unloading in the muscle based on the Piiper's model. The hatching and dotting denote range of predominant diffusion and perfusion limitation, respectively. See the text for the details.

during maximal intensity exercise (Gayeski et al., 1988; Groebe and Thews, 1987; Honig et al., 1984), the expression can therefore be simplified as:

$$\dot{\mathbf{V}}_{\mathrm{T}}\mathbf{O}_{2}\max = \mathbf{O}_{2} \cdot \text{delivery}^{"} - \dot{\mathbf{Q}}_{\mathrm{T}} \cdot [\mathrm{Hb}] \cdot \boldsymbol{\alpha} \cdot \boldsymbol{\lambda} \mathrm{v} \cdot \mathrm{PvO}_{2}$$
$$= \mathbf{D}_{\mathrm{T}} \cdot \mathbf{k} \cdot \mathrm{PvO}_{2}. \qquad [\mathrm{Eq.9}]$$

As seen in Fig.6, peak  $\dot{V}O_2$  in the tissue ( $\dot{V}_TO_2$ max) should be determined as to satisfy both convective curve and diffusive line in Eq.9 on the  $\dot{V}_TO_2$ -PO<sub>2</sub> plot. Using this plot, from the latter half of 1980s, Wagner, Hogan, and their associates have repeatedly measured the  $\dot{V}_T O_2$  max under several systematic manipulated conditions such as hypoxia/hyperoxia, CO inhalation, blood infusion/withdrawal and so on, to clarify the relative contribution of diffusive and convective factors limiting the  $\dot{V}_T O_2$ max (Hogan et al., 1989; Hogan et al., 1990a; Hogan et al., 1990b; Hogan et al., 1991a; Hogan et al., 1991b; Roca et al., 1989; Roca et al., 1992; Schaffartzik et al., 1993; Torre-Bueno et al., 1985; also see Wagner, 1988 and Wagner, 1991 for review). Their studies always resulted in that  $\dot{V}_{\scriptscriptstyle T}O_{\scriptscriptstyle 2}max$  located along on the same diffusive flux line (i.e., the last term in Eq.9) passing through the origin under the manipulated conditions in which only one variable was altered systematically (such as increase/decrease of PIO<sub>2</sub>, for example) in both intact humans and isolated canine muscles. Surprisingly, even if  $O_2$ -delivery was set as the same by the artificial manipulation of blood flow and O<sub>2</sub> content in dog gastrocnemius in situ, the plotted line still passed through the origin (Hogan et al., 1989).

 $\dot{V}_T O_2 max$  is determined by the interaction between the convective  $O_2$  delivery by capillary blood flow (Fick's equation) and 'effective' diffusion of O<sub>2</sub> from the erythrocytes to the mitochondria (Low of diffusion). The O<sub>2</sub> delivery which depends on  $\dot{Q}_T$ , SaO<sub>2</sub> and [Hb], is important in determining  $\dot{V}_T O_2$  max primarily because  $O_2$ delivery largely determines  $P\overline{mc}O_2$ . For example, with decreased  $O_2$  delivery,  $P\overline{mc}O_2$  is decreased and  $\dot{V}_T O_2$  max will decline because of the reduced PO<sub>2</sub> gradient. Therefore, the  $O_2$  diffusion remains an essential determinant of  $\dot{V}_TO_2max$  as  $O_2$  delivery altered, although still subject to some assumptions concerning heterogeneity and O<sub>2</sub> shunt. Of course, all components of the  $O_2$  transport pathway by affecting either  $O_2$  delivery or O<sub>2</sub> diffusion have a direct role in setting actual  $\dot{V}_TO_2$ max. For any given  $O_2$  delivery, however, probably O<sub>2</sub> diffusion sets maximal O<sub>2</sub> flow to mitochondria (Roca et al., 1989).

Using same experimental strategy, Kohzuki and his associates, recently, have also demonstrated that the line of the  $\dot{V}_TO_2$  with altered  $PvO_2$  by artificial systematic manipulations had a positive intercept on  $\dot{V}_TO_2$ -PO<sub>2</sub> plot, not through the origin (Kohzuki et al., 1993a; Kohzuki et al., 1993b; Kohzuki et al., 1994). Their results from rest to maximal electrical stimulation to the isolated dog gracilis or gastrocnemius muscles *in situ* hypothesized that  $\dot{V}_TO_2$  could consisted both of the  $O_2$ -delivery limited component as indicated by the line of  $\dot{V}_TO_2$ -PO<sub>2</sub>, and the O<sub>2</sub>-diffusion limited component which corresponded to the amount of the intercept of the line.

# b) Application of Piiper's model to tissue diffusion/convection interaction

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Fig. 6 Graphical representation of tissue oxygen uptake  $(\dot{V}_{\tau}O_2)$  with venous effluent PO<sub>2</sub> (PvO<sub>2</sub>) determined by both convective and diffusive O<sub>2</sub> flux (Eq.8).

As one of the quantitative analyses is to clarify the relative contribution of diffusive and convective factors limiting  $\dot{V}_T O_2$ max, the same strategy for the lung carried out by Piiper's group (described in the section 5) can be adopted essentially (Fukuba, 1992). Namely, under the same assumptions as those in the case of the lung, the infinitesimal diffusive and convective  $O_2$  flow at any point x along the gas exchanger pathway in the muscle (total length;  $x_0$ ) is expressed as:

$$d\dot{M}(x) = \dot{Q}_{T} \cdot [-dC(x)], \qquad [Eq.10]$$

and

$$d\mathbf{\dot{M}}(\mathbf{x}) = [PmcO_2(\mathbf{x}) - PmO_2] \cdot dD_T(\mathbf{x}), \qquad [Eq.11]$$

where  $d\dot{M}(x)$  is tissue  $O_2$  uptake from capillary blood in the infinitesimal cross-sectional element at x, -dC(x) is infinitesimal decrease of  $O_2$  content in muscular capillary blood, and  $dD_T(x)$  is diffusion from capillary blood to mitochondrion across the infinitesimal element of the diffusion barrier (see Fig.7). Solving both equations (refer Piiper and Scheid, 1981 for the detailed method), the muscular capillary  $PO_2$  at x,  $PmcO_2(x)$  is:

$$\begin{split} & [\operatorname{PmcO}_2(\mathbf{x}) - \operatorname{PmO}_2] / [\operatorname{PaO}_2 - \operatorname{PmO}_2] \\ & = & \exp[-\{\operatorname{D}_{\mathrm{T}}/(\dot{\mathbf{Q}}_{\mathrm{T}} \cdot \boldsymbol{\beta})\} \cdot (\mathbf{x}/\mathbf{x}_0)], \end{split} \qquad \qquad [\operatorname{Eq.12}] \end{split}$$

As the same as in the pulmonary capillary  $PO_2$  (Fig.5a), the  $PO_2$  in muscular capillary blood (i.e.,  $PmcO_2(x)$ ) also declines from artery to end-capillary in an exponential manner. This equation also predicts the muscular endcapillary (i.e.,  $PmcO_2(x_0) = PvO_2$  at  $x = x_0$ ),

$$[PaO_2 - PvO_2] / [PaO_2 - PmO_2] = 1 - exp[-\{D_T / (\dot{Q}_T \cdot \beta)\}].$$
 [Eq.13]

This equation shows "the completeness of equilibration achieved" which is exactly determined by the ratio:  $D_T/(\dot{Q}_T \cdot \beta)$  (Fig.5b). As seen in Fig.5b, the consequent  $O_2$ unloading from blood to muscle is achieved in proportion to the increase of  $D_T/(\dot{Q}_T \cdot \beta)$  ratio.

The equilibrium in terms of the pressure gradient from capillary blood to muscular mitochondria surely depends on the time available, because the muscular



Fig. 7 Model used for the analysis of muscular capillary to mitochondrial equilibration of  $O_2$ .

blood flow  $(\dot{Q}_T)$  can be expressed as:

$$\dot{\mathbf{Q}}_{\mathrm{T}} = \mathbf{V}_{\mathrm{M}} / \mathrm{MTT}_{\mathrm{M}}, \qquad [\mathrm{Eq.14}]$$

where  $V_M$  and  $MTT_M$  are the volume and mean transit time for the blood in the muscular capillary bed. Therefore, the ratio:  $D_T/(\dot{Q}_T \cdot \beta)$  can be rewritten as,

$$[D_{T}/(\dot{Q}_{T}\cdot\boldsymbol{\beta})] = D_{T}\cdot MTT_{M}/(V_{M}\cdot\boldsymbol{\beta}).$$
 [Eq.15]

Furthermore, the time constant ( $\tau$ ) can be applied as an analogy to RC electric circuit for the diffusive resistance (R=1/D<sub>T</sub>) and capillary capacitance (C= $\beta$ ·V<sub>M</sub>), that is:

$$\tau = \mathbf{R} \cdot \mathbf{C} = (1/\mathbf{D}_{\mathrm{T}}) \cdot (\boldsymbol{\beta} \cdot \mathbf{V}_{\mathrm{M}}). \qquad [\mathrm{Eq.16}]$$

The time constant,  $\tau$  corresponds to the velocity for recharging muscular mitochondrial O<sub>2</sub>. Unfortunately, although there is no appropriate physiological values of D<sub>T</sub> and V<sub>M</sub> to calculate the realistic  $\tau$  such as in the case of lung in section 5, at least it can be noticed that as for the example, at  $\tau$ , (PvO<sub>2</sub>-PmO<sub>2</sub>)/(PaO<sub>2</sub>-PmO<sub>2</sub>) will be 0.33, and at  $\tau \times 3$ , the pressure gradient from muscular end-capillary end to mitochondria will be only 5% of the initial one: (PaO<sub>2</sub>-PmO<sub>2</sub>). From Eqs.15 and 16, the essential determinant factor of the O<sub>2</sub>-unloading to muscular mitochondria, in other words, of "the completeness of equilibrium achieved" in peripheral site is expressed as:

$$[D_{\rm T}/(\dot{\mathbf{Q}}_{\rm T}\cdot\boldsymbol{\beta})] = MTT_{\rm M}/\boldsymbol{\tau}.$$
 [Eq.17]

This equation means, as for example, for  $(PvO_2 - PmO_2)$  to be 5% of  $(PaO_2 - PmO_2)$ ,  $MTT_M$  or  $D_T/(\dot{Q}_T \cdot \beta)$  should be same as  $\tau \times 3$  (Fig.8). In addition, the essential interaction factor:  $D_T/(\dot{Q}_T \cdot \beta)$  is determined by the balance



Fig. 8 "The completeness of equilibration achieved" for  $O_{2^{-1}}$  unloading in muscle plotted against the diffusive/convective interaction factor:  $\dot{D}_{T}/(\dot{Q}_{T} \cdot \beta)$  and its equivalent:  $MTT_{M}/\tau$  where  $\tau = \beta \cdot V_{M}/D_{T}$ .

between the structural variables of  $D_T$  and  $V_M$ , and the functional variable of  $MTT_M$ .

At the end of muscular capillary blood, the factors which might be expected to elevate and influence  $PvO_2$  in maximal exercise, would be 1) hyper-perfusion, 2) diffusion limitation, 3) blood flow heterogeneity, and 4)  $\dot{V}_TO_2/\dot{Q}_T$  mismatching (Piiper, 1990; Piiper and Haab, 1991).

### Bohr effect to muscular O<sub>2</sub>-unloading

As seen in Fig.6,  $\dot{V}_TO_2$  benefits from  $PvO_2$  decreasing more from a convective viewpoint, but from a diffusive perspective it needs to decrease less. Thus the decrease in  $\lambda v$  should be maximized: this is achieved by a rightward shift of the  $O_2$ -DC. The dominant factor shifting this curve to the right during severe and maximal exercise is the fall of the pH (i.e., Bohr effect). Wasserman and his associates have recently demonstrated repeatedly the important finding that this shift actually maintains  $PvO_2$  at a relatively constant value of approximately 15-20 torr in humans (Stringer et al., 1994; see Wasserman et al., 1991 and Wasserman, 1994 for review).

What degree of  $O_2$ -unloading does Bohr effect affect and facilitate in the peripheral muscular site ? Severinghaus (1994) has tried to answer this question by the model incorporating the standard equations under the reasonable assumptions. The model analysis suggested that the Bohr effect contributed 15-30 % to  $\dot{V}O_2$ max and kept  $PvO_2$  almost constant as work rate increased from 60 to 100 % of  $\dot{V}O_2$ max.

In addition to the metabolic acidosis *per se*, ventilatory control is also known as an important modulator of arterial pH. By the integration of the Henderson-Hasselbalch and alveolar air equations (Whipp and Ward, 1994), the arterial pH can be expressed as,



Fig. 9 A schematic representation of the role of the respiratory compensation for the metabolic acidosis (\*RCMA) on muscular  $O_2$ -unloading via the Bohr effect.

$$pHa = pK' + log\{([HCO_3^-]_a/25.8) \cdot (\dot{V}_E/\dot{V}_pCO_2) \cdot (1 - V_D/V_T)\}$$
  
[Eq.18]

where pK'=6.1,  $[HCO_3^{-}]_a$  is the arterial bicarbonate concentration,  $\dot{V}_E$  is the pulmonary ventilation,  $\dot{V}_pCO_2$  is the pulmonary  $CO_2$  output, and  $V_D/V_T$  is the dead space to tidal volume ratio. This equation shows three distinct components which affect the pHa: 1) the acid-base setpoint component;  $[HCO_3^{-}]_a$ , 2) the respiratory control component;  $\dot{V}_E/\dot{V}_PCO_2$ , and 3) the ventilatory efficiency;  $(1-V_D/V_T)$ . That is, the reduction in arterial (and hence muscle capillary) pH will be attenuated by the degree of respiratory compensation for the metabolic acidosis if  $V_D/V_T$  can be assumed to be same within the severe and maximal exercise range (see Fig.9).

Therefore, Fukuba and Whipp (1995) have modelled the influence on muscular end-capillary pH (pHv) and  $PO_2$  (PvO<sub>2</sub>) of the Bohr shift interaction between the exercise-induced acidemia and the compensatory hyperventilation using standard relationships for O<sub>2</sub>-DC and the Bohr influences and also the blood CO<sub>2</sub> dissociation curve and its Haldane effect.



Fig. 10 Computed values of pHv and  $PvO_2$  within the specified physiological range of  $[HCO_3^-]_a$  and  $\dot{V}_E/\dot{V}_PCO_2$ . The dots represent typical values at maximal exercise, i.e.,  $[HCO_3^-]_a$  and  $\dot{V}_E/\dot{V}_PCO_2$  are 14 (mEq/l) and 30 (l/l), respectively (redrawn from Fukuba and Whipp, 1995).

Consequently, in addition to the well recognized effect of the metabolic acidosis on pHv and PvO<sub>2</sub> during maximal exercise, it has been confirmed that ventilatory control also had a significant modulating effect on pHv and PvO<sub>2</sub> (Fig.10). If the respiratory compensation for the metabolic acidosis ( $\dot{V}_{\rm E}/\dot{V}_{\rm P}CO_2$ ) is below the normal ventilatory response range (<30), e.g., as a result of insensitive ventilatory control mechanisms, pHv decreased more severely - to values of 7.0 or less. On the other hand, if the compensatory hyperventilation results in values of  $\dot{V}_{\rm E}/\dot{V}_{\rm P}CO_2$  above 30, the degree of the lowering of PvO<sub>2</sub> was significantly smaller than that of hypoventilatory range ( $\dot{V}_{\rm E}/\dot{V}_{\rm P}CO_2 < 30$ ). These results show that the compensatory hyperventilation during

maximal exercise attenuates the acidemia while also helping maintain the muscle capillary  $PO_2$  level, i.e., in addition to the Bohr effect.

#### Other potential factors

In this last section, we briefly summarize the other two potential evidences which have been pointed out recently regarding the factors limiting  $\dot{V}O_2max$ .

For a long time, it has been believed that there is no serious cause limiting  $\dot{V}O_2max$  within the respiratory system, because the maximum voluntary ventilation (MVV) is sufficiently high to the hyperventilation in normal subject during severe and maximal exercise.

Furthermore, even if the  $PaO_2$  slightly decreases due to the constrained ventilation by some reason,  $CaO_2$  level in Fick's equation is well maintained by the flat region of  $O_2$ -DC.

Dempsey and his associates (Dempsey et al., 1984; Dempsey and Fregosi, 1985; Powers et al., 1989), however, the athletes who have greater [Hb] and increased  $O_2$ -carrying capacity (for example, the  $\dot{V}O_2$ max>70 ml· min<sup>-1</sup>·kg<sup>-1</sup>), sometimes showed marked arterial desaturation and severe fall in PaO<sub>2</sub> around 60 torr, namely the hypoxemia, during maximal exercise at sea-level, with little or no alveolar hyperventilation.

Whereas several factors are postulated as the reason of this hypoxemia such as  $\dot{V}_A/\dot{Q}$  mismatching, a-v shunt and hypoventilation, they have considered to be caused mainly by the diffusion limitation. It is related to the extremely high pulmonary blood flow (also refer to section 5) and the accompanied short pulmonary transit time  $(MTT_L)$  below the critical one (about 0.3 to 0.5 sec) to sufficiently achieve the oxygenation in arterial red blood cells. This is due probably to that the pulmonary capillary beds are already recruited maximally (i.e, the maximally pulmonary capillary blood volume: V<sub>L</sub>) at the point of Q exceeding around 25 1/min before the attainment of Qmax for the 'extremely' fit subject. That is, MTT<sub>L</sub> at maximal exercise (MTT<sub>L</sub> =  $V_L/\dot{Q}max$ ), becomes below the critical time before the maximal exhaustion.

The other important factor might be the magnitude of the hyperventilation which is insufficient due mainly to the pulmonary mechanical limit in such fit subject (Whipp and Pardy, 1987). In any case, the incidence of such hypoxemia among the 'extremely' fit subjects is still unknown because not enough athletes have been investigated.

It should be emphasized from the findings of the athlete's hypoxemia that the hypothesized "symmorphosis" is clearly inapplicable to the human pulmonary system because of its failure to improve its function along with other cardiovascular and muscular functional improvements with a physical training (also see Weibel and Kayar, 1988).

Saltin and his associates have investigated the relationship between the muscular mass engaged in exercise and the  $\dot{V}O_2max$  (Andersen and Saltin, 1985; Saltin, 1985; Rowell et al., 1986). When the human subject performs the leg maximal exercise, the additional arm exercise to the leg exercise causes no further increase in  $\dot{Q}max$  and  $\dot{V}O_2max$ . This simple but excellent result indicates that  $\dot{V}O_2max$  does not depend on the muscular mass, and  $\dot{V}O_2max$  appears merely when the critical muscular mass (50-60% of total mass ?) is active. In addition, it also gives one of the good evidences that there is no serious limiting factor within the metabolic process in the working muscle (see also Saltin and Gollnick, 1983).

When a relatively small fraction of muscular mass to total mass was engaged in exercise, for example, one-leg quadriceps during dynamic knee extension exercise, both  $\dot{Q}_T$  and  $\dot{V}_T O_2$  of quadriceps at exhaustion showed a surprisingly high, compared with those observed as part of the whole body maximal exercise. This indicates that, at the maximal exercise engaged in relatively large mass of the muscles (so-called, 'systemic'), the blood flow to each working muscle region is relatively insufficient due to the restriction of the distribution of cardiac output. Namely, the maximum ability inherent in each muscle itself does not exert fully during the systemic maximal exercise. Therefore, it is one of the key mechanisms to optimize the distribution of the blood flow at VO<sub>2</sub>max. The regulatory mechanism is, however, too complex. At the maximum of the whole body exercise, the distribution of the systemic blood flow is constrained by the vasoconstriction via the central sympathetic nervous control, whereas the peripheral working muscular capillary is vasodilated by the local metabolic mediation. Unfortunately, the current understandings are not enough to lead the appropriate explanation to the underlying mechanisms.

#### **Concluding remarks**

The  $\dot{V}O_2$ max which is defined as the maximum  $O_2$ flow from ambient air to mitochondria in working muscle, is firstly limited sometimes for the 'extremely' fit athletes by the convective ventilation. The next important step exists in the barrier from alveolar gas to blood, consequently the arterial  $O_2$  level is determined by the diffusive and convective interaction in the lung. The arterial  $O_2$  is transferred to the working muscular region both by the systemic and peripheral circulatory regulation. Finally, in the barrier of the blood to mitochondria, the amount of  $O_2$  which can be attained to the chemical reaction in mitochondrial cristae is determined by the diffusive and convective interaction in the muscle.

According to such sequence, we should take into account what limits and determines the  $\dot{V}O_2$ max which is altered either by the acute exposures with mainly the functional modification (for example, such as change of PIO<sub>2</sub>, blood infusion/withdrawal, and sympathetic nerves blocking), or by the chronic exposures with both functional and structural modifications (such as physical conditioning and chronic hypoxia).

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### **General Abbreviations**

 $\dot{V}O_2$  (or  $\dot{V}_pO_2$ ) and  $\dot{V}_TO_2$ : oxygen (O<sub>2</sub>) uptake in the lung and working muscular tissue.

 $\dot{Q}$  (or  $\dot{Q}_p$ ) and  $\dot{Q}_T$ : the cardiac output in the lung and the muscular blood flow.

 $D_{\rm p}$  and  $D_{\rm T}$ : a pulmonary diffusing capacity and an 'effective' (or 'apparent') capillary-to-mitochondrial diffusion capacity.

 $\dot{V}_{\text{I}},~\dot{V}_{\text{E}},$  and  $\dot{V}_{\text{A}}\text{:}$  Inspired, expired, and alveolar ventilation.

 $PIO_2$ ,  $PAO_2$ ,  $PaO_2$ ,  $P\overline{pc}O_2$ ,  $P\overline{mc}O_2$ ,  $P\overline{v}O_2$ ,  $PvO_2$ , and  $PmO_2$  (or  $PmitO_2$ ): Inspired, alveolar, arterial, meanpulmonary capillary, mean-muscular capillary, mixedvenous, muscular end-capillary, and mitochondrial  $PO_2$ .

CIO<sub>2</sub>, CEO<sub>2</sub>, CAO<sub>2</sub>, CaO<sub>2</sub>,  $C\overline{v}O_2$ , and  $CvO_2$ : O<sub>2</sub> content in inspired, expired, and alveolar gases and in arterial, mixed venous, and muscular end-capillary bloods.

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