METABOLIC AND CIRCULATORY LIMITATIONS TO $\dot{V}_{O_2}\text{max}$ AT THE WHOLE ANIMAL LEVEL

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SUMMARY

The $O_2$ path from environment to mitochondria can be viewed as a cascade of resistances in series, each being overcome by a specific pressure gradient ($O_2$ conductance equation). To assess the relative importance of the different factors that can set a limit to $V_{O_2}\text{max}$, three sets of resistances will be identified, $R_Q$, $R_c$ and $R_m$, inversely proportional to: $O_2$ transport ($Q_{\text{max}} \times [\text{Hb}]$), $R_Q$; capillary cross section, $R_c$; and succinic dehydrogenase (SDH) activity, $R_m$. Published data show that changes of $V_{O_2}\text{max}$ can be induced by altering the blood $O_2$ capacity, or by training, and that these changes are accompanied by measured changes of the above identified resistances. From these data, the ratio of each resistance to the overall resistance can be calculated by algebraic manipulation of the $O_2$ conductance equation, expressed in relative form. It can thus be shown that: (1) in two-legged exercise, about 75% of $V_{O_2}\text{max}$ is set by $O_2$ transport, the remaining fraction being about equally partitioned between the two peripheral factors indicated above, and that (2) in one-legged exercise, the limits to $V_{O_2}\text{max}$ are about equally set by central and peripheral factors.

Maximal $O_2$ consumption ($\dot{V}_{O_2}\text{max}$) increases with increasing $O_2$ partial pressure in inspired air (Bannister & Cunningham, 1954; Fagraeus, Karlsson, Linnarsson & Saltin, 1973; Kaijser, 1970; Margaria, Camporesi, Aghemo & Sassi, 1972; Margaria, Cerretelli, Marchi & Rossi, 1961; Nielsen & Hansen, 1937; Welch & Pedersen, 1981) and following the transfusion of red blood cells (Buick et al. 1980; Ekblom, Goldbarg & Gullbring, 1972; Ekblom, Wilson & Åstrand, 1976); it decreases in hypoxia (both acute and chronic) (see Cerretelli, 1981 for review), following CO inhalation (Ekblom & Huot, 1972; Ekblom, Huot, Stein & Sthorstenson, 1975; Pirnay, Dujardin, Deroanne & Petit, 1971; Raven et al. 1974; Vogel & Gleser, 1972) and after acute anaemia (Woodson, Wills & Lenfant, 1978).

It is generally inferred from these data that, at sea level, $V_{O_2}\text{max}$ is limited essentially by the $O_2$ transport system (cardiac output times blood $O_2$-carrying capacity). However, several other factors, such as peripheral circulation, $O_2$ diffusion at the muscle level and mitochondrial capacity, have also been considered among the

Key words: $V_{O_2}\text{max}$ limitations, blood infusion, two-legged vs one-legged training.
possible factors that set a limit to $\dot{V}_{O2\text{max}}$, particularly during exercise with small muscle groups (see for instance, Kaijser, 1970; Saltin, 1977).

The following article is devoted to a discussion of the factors limiting $\dot{V}_{O2\text{max}}$.

The $O_2$ path from the environment to the mitochondria can be viewed as a cascade of resistances in series, each individual resistance ($R_i$) being overcome by a specific $O_2$ pressure gradient ($\Delta P_i$). In this model, the $O_2$ flow through each section is equal to the overall flow through the system, and the overall resistance, $R_T$, is given by the sum of the $n$ resistances in series:

$$\dot{V}_{O2} = \frac{\sum_{i=1}^{n} \Delta P_i}{\sum_{i=1}^{n} R_i} = \frac{\Delta P_T}{R_T},$$

where $\Delta P_T$ is the overall $O_2$ pressure gradient from the environment to the mitochondria.

Equation 1 can be utilized to calculate each individual $R_i$, provided that the corresponding pressure gradient can be measured, or estimated. However, the procedure requires several assumptions and complex calculations (Shephard, 1976).

A somewhat different approach is developed here. Published values of the change in $\dot{V}_{O2\text{max}}$, induced by altering acutely the blood $O_2$ capacity or by training, and resulting from (or accompanied by) measured changes of other physiological parameters that can be likened to individual resistances, are entered into equation 1 expressed in relative form. It is then possible to calculate the ratio of each individual $R_i$ to the overall resistance $R_T$.

**THEORY**

As a first approximation, when exercising at $\dot{V}_{O2\text{max}}$, equation 1 becomes:

$$\dot{V}_{O2\text{max}} = \frac{\Delta P_T}{R_T} = \frac{\Delta P_T}{R_Q + R_c + R_m},$$

where the following three individual resistances have been identified.

(1) $R_Q$, inversely proportional to maximal cardiac output and to the average slope of the blood $O_2$ dissociation curve.

(2) $R_c$, inversely proportional to peripheral diffusion and perfusion, which in turn depend on the $O_2$ diffusion coefficient from the capillary to the cells, on the surface and volume of the capillary bed, and on the average distance between capillary and cell.

(3) $R_m$, inversely proportional to mitochondrial $O_2$ utilization capacity. The latter depends on the molecular conductance for $O_2$, the surface of the inner mitochondrial membrane, and on the total volume of mitochondria.

The reader is referred to Taylor & Weibel (1981), for a detailed discussion of the physiological and morphological parameters on which $R_Q$, $R_c$ and $R_m$ depend, and to
Table 1. Average effects on the indicated number of subjects (N) of withdrawal or infusion of red blood cells (or blood) on $\dot{V}_{O_2,\text{max}}$ (1 min$^{-1}$), $\dot{Q}_{\text{max}}$ (1 min$^{-1}$) and [Hb] (g dl$^{-1}$), taken from the quoted references

<table>
<thead>
<tr>
<th>Reference</th>
<th>$\dot{V}_{O_2,\text{max}}$</th>
<th>$\Delta \dot{V}_{O_2,\text{max}}$</th>
<th>$\dot{Q}_{\text{max}}$</th>
<th>$\Delta \dot{Q}_{\text{max}}$</th>
<th>[Hb]</th>
<th>$\Delta$ [Hb]</th>
<th>$\Delta$ RQ/RQ</th>
<th>N</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buick et al. (1980)</td>
<td>5·33</td>
<td>+ 0·25</td>
<td>-</td>
<td>-</td>
<td>15·1</td>
<td>+ 1·2</td>
<td>-0·080</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4·85</td>
<td>+ 0·26</td>
<td>-</td>
<td>-</td>
<td>15·8</td>
<td>+ 0·9</td>
<td>-0·057</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ekblom, Goldbarg &amp; Gullbring (1972)</td>
<td>4·57</td>
<td>- 0·48</td>
<td>-</td>
<td>-</td>
<td>14·6</td>
<td>- 1·9</td>
<td>0·130</td>
<td>3</td>
<td>Subsequent withdrawals (at 2-day intervals) of 400, 800 and 1200 ml blood</td>
</tr>
<tr>
<td></td>
<td>4·49</td>
<td>+ 0·39</td>
<td>-</td>
<td>-</td>
<td>13·2</td>
<td>+ 1·7</td>
<td>-0·129</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4·49</td>
<td>- 0·28</td>
<td>-</td>
<td>-</td>
<td>14·9</td>
<td>- 1·6</td>
<td>0·107</td>
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</tr>
<tr>
<td></td>
<td>4·49</td>
<td>- 0·46</td>
<td>-</td>
<td>-</td>
<td>14·9</td>
<td>- 2·3</td>
<td>0·154</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4·49</td>
<td>- 0·71</td>
<td>-</td>
<td>-</td>
<td>14·9</td>
<td>- 2·7</td>
<td>0·221</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ekblom, Wilson &amp; Astrand (1976)</td>
<td>4·27</td>
<td>- 0·24</td>
<td>28·7</td>
<td>+ 0·8</td>
<td>15·4</td>
<td>- 1·6</td>
<td>0·079</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4·27</td>
<td>+ 0·34</td>
<td>28·7</td>
<td>- 0·4</td>
<td>14·7</td>
<td>+ 1·4</td>
<td>-0·080</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Woodson, Wills &amp; Lenfant (1978)</td>
<td>43·1</td>
<td>- 12·4</td>
<td>284</td>
<td>- 21</td>
<td>15·3</td>
<td>- 5·3</td>
<td>+ 0·395</td>
<td>4</td>
<td>Established anaemia. Not included in Fig. 1</td>
</tr>
</tbody>
</table>

In the experiments of Woodson, Wills & Lenfant (1978) $\dot{V}_{O_2,\text{max}}$ and $\dot{Q}_{\text{max}}$ are given in ml kg$^{-1}$ min$^{-1}$ and refer to conditions of established anaemia. Other reported data were measures immediately before, and within 2 days after, the experimental manipulation.

$\Delta$ RQ/RQ is the relative change of the resistance to O$_2$ transport calculated from the product $\dot{Q}_{\text{max}}$·[Hb], when available, or from [Hb] alone, an increase of O$_2$ transport capacity leading to a negative value of $\Delta$ RQ/RQ.

The data obtained by Woodson et al. (1978) were not included in Fig. 1 since in conditions of established anaemia, the two peripheral resistances $R_c$ and $R_m$ may also have changed (see text for details).
Shephard (1969, 1976) for an analytical formulation of the corresponding pressure gradients.

Endurance training, or acute alterations of blood O₂ capacity, lead, as is well known, to changes of \( \dot{V}_O_2 \text{max} \). Under these conditions, *ceteris paribus*, the overall pressure gradient cannot be expected to change (\( \Delta P_T = \text{constant} \)). Hence, assuming that the system behaves linearly, the changes of \( \dot{V}_O_2 \text{max} \) must be due to an equal (and opposite) change of the total resistance to flow:

\[
\dot{V}_O_2 \text{max} + \Delta \dot{V}_O_2 \text{max} = \frac{\Delta P_T}{R_T + \Delta R_T}.
\]

Dividing equation 3 by equation 2 and rearranging:

\[
\frac{\dot{V}_O_2 \text{max} + \Delta \dot{V}_O_2 \text{max}}{\dot{V}_O_2 \text{max}} = \frac{1}{1 + \Delta R_T/R_T}.
\]

Since \( \Delta R_T = \Delta R_Q + \Delta R_c + \Delta R_m \), equation 4 becomes:

\[
\frac{\dot{V}_O_2 \text{max} + \Delta \dot{V}_O_2 \text{max}}{\dot{V}_O_2 \text{max}} = \frac{1}{1 + \frac{\Delta R_Q}{R_T} + \frac{\Delta R_c}{R_T} + \frac{\Delta R_m}{R_T}},
\]

which can be written in the equivalent form:

\[
\frac{\dot{V}_O_2 \text{max} + \Delta \dot{V}_O_2 \text{max}}{\dot{V}_O_2 \text{max}} = \frac{1}{1 + \frac{R_Q}{R_T} \cdot \frac{\Delta R_Q}{R_Q} + \frac{R_c}{R_T} \cdot \frac{\Delta R_c}{R_c} + \frac{R_m}{R_T} \cdot \frac{\Delta R_m}{R_m}}.
\]

By setting \( \frac{R_Q}{R_T} = F_Q \), \( \frac{R_c}{R_T} = F_c \), and \( \frac{R_m}{R_T} = F_m \), equation 5’ becomes:

\[
\frac{\dot{V}_O_2 \text{max} + \Delta \dot{V}_O_2 \text{max}}{\dot{V}_O_2 \text{max}} = \frac{1}{1 + F_Q \cdot \frac{\Delta R_Q}{R_Q} + F_c \cdot \frac{\Delta R_c}{R_c} + F_m \cdot \frac{\Delta R_m}{R_m}}.
\]

Thus, in equation 6, the three terms \( F_Q \), \( F_c \) and \( F_m \) indicate the fractional limitations of \( \dot{V}_O_2 \text{max} \) due to O₂ transport, peripheral perfusion and diffusion and mitochondrial capacity, respectively; while \( \Delta R_Q/R_Q \), \( \Delta R_c/R_c \) and \( \Delta R_m/R_m \) are the relative
changes of the appropriate resistances. The resistances will be assumed to be inversely proportional:

(i) RQ, to maximal cardiac output (Qmax) times blood Hb concentration:

\[ RQ = \frac{kQ}{Q_{\text{max}} \times [Hb]} \quad ; \quad (7) \]

(ii) Rc, to capillary cross sectional area:

\[ Rc = \frac{kc}{\text{capillary cross section}} \quad ; \quad (8) \]

(iii) Rm, to mitochondrial SDH activity:

\[ Rm = \frac{km}{\text{SDH}} \quad . \quad (9) \]

When considering only the relative changes of resistance, as is the case in equation 6, the three constants kQ, kc and km cancel out. However, they have to be introduced for dimensional uniformity and they can be assigned, conventionally, the value of 1.0.

The changes of Qmax, [Hb], capillary cross section and SDH activity, elicited by appropriate experimental manipulations or by training, will be entered into equation 6 together with the corresponding changes of VO2max. As detailed in the next section it will then become possible to estimate FQ, Fc and Fm from published data.

In this approach, it is assumed that pulmonary ventilation and lung diffusion are not among the major limiting factors, which seems justified for healthy subjects at sea level (Shephard, 1971).

It is interesting to note that the control of metabolic pathways has been analysed in a similar way by Kacser & Burns (1973, 1979). These authors define as 'sensitivity coefficient', Z, the very analogue of the quantity which is here defined as 'fractional limitation' of VO2max, and given the symbol F.

**CALCULATIONS**

This section is devoted to an attempt to calculate the fractional limitations of VO2max due to O2 transport (FQ), peripheral perfusion and diffusion (Fc) and mitochondrial capacity (Fm) as from published data. Firstly, FQ will be estimated from the results of experiments in which the blood O2-carrying capacity was acutely altered by withdrawal, or infusion, of red blood cells (or blood) and the resulting changes of VO2max measured. Secondly, the three fractional limitations, FQ, Fc and Fm, will be estimated from the changes of VO2max elicited by training and from the accompanying measured changes of maximal cardiac output, capillary cross sectional area and mitochondrial capacity.
The changes in $\dot{V}_{O_2}\text{max}$ resulting from manipulation of the blood are indicated in Table 1, together with the corresponding changes of Hb concentrations and, when available, of $Q_{\text{max}}$, as from the data of Buick et al. (1980); Ekblom et al. (1972, 1976) and Woodson et al. (1978). The corresponding changes of the resistance to $O_2$ transport, $\Delta RQ/RQ$ are also given. Since the experiments were done acutely, the other two sets of resistances ($R_c$ and $R_m$) can reasonably be assumed not to change significantly. Hence $\Delta R_c = \Delta R_m = 0$, so that equation 6, once rearranged reduces to:

$$\frac{\dot{V}_{O_2}\text{max}}{\dot{V}_{O_2}\text{max} + \Delta \dot{V}_{O_2}\text{max}} = 1 + FQ \frac{\Delta RQ}{RQ}.$$  \hspace{1cm} (10)

Fig. 1. Average changes of $\dot{V}_{O_2}\text{max}$ are plotted as a function of the changes of the resistance to $O_2$ transport, from the data of Table 1. The slope of the regression is the fractional limitation of $\dot{V}_{O_2}\text{max}$ due to $O_2$ transport, $FQ = 0.775$ (see text, equations 10 and 11). For references, see Table 1. $y = 1.003 + 0.775x$ ($r^2 = 0.98$).
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Least squares linear regression of the data of Table 1 yields (see Fig. 1):

\[ y = 1.003 + 0.775x, \]  

\[(r = 0.99; \ N = 9; \ P < 0.001) \text{ where } y = \dot{V}_{O_2}\text{max}/(\dot{V}_{O_2}\text{max} + \Delta\dot{V}_{O_2}\text{max}) \text{ and } x = \Delta RQ/RQ. \] Thus \( FQ = 0.78 \).

From this first series of calculations it can then be concluded that the limitation of \( \dot{V}_{O_2}\text{max} \) due to \( O_2 \) transport (\( \dot{Q}_{\text{max}} \) times blood \( O_2 \) capacity) amounts to about 80\% under these experimental conditions.

The percentage increase with training of: (1) \( \dot{V}_{O_2}\text{max} \), (2) mitochondrial SDH activity, (3) capillary cross section per unit muscle surface and (4) maximal cardiac output are presented in Fig. 2, for two-legged (cycling) endurance training in man as from several sources (Andersen & Henriksson, 1977; Henriksson & Reitman, 1976, 1977; Ekblom et al. 1968; Saltin et al. 1968). (For a comprehensive review of skeletal muscle adaptations to training, see Saltin & Gollnick, 1983.) The subjects’ mean increase in \( \dot{V}_{O_2}\text{max} \) amounts to 18\%, while the corresponding increase in enzymatic activity amounts to 31.2\%, of capillary cross sectional area to 20\% and of maximal cardiac output to 11.3\%. Thus: \( (\dot{V}_{O_2}\text{max} + \Delta\dot{V}_{O_2}\text{max})/\dot{V}_{O_2}\text{max} = 1.180, \Delta Rm/Rm = -0.312; \Delta Rc/Rc = -0.200 \) and \( \Delta RQ/RQ = -0.113 \). Inserting these values into equation 9, and rearranging, one obtains:

\[ 0.132Fm + 0.200Fc + 0.113FQ = 0.1525. \]  

(12)

If it assumed that no other limiting factors exist besides the three considered,

\[ Fm + Fc + FQ = 1.0, \]  

(13)

Table 2. Fractional limitations of \( \dot{V}_{O_2}\text{max} \), during one- and two-legged maximal exercise, due to: (1) \( O_2 \) transport (\( \dot{Q}_{\text{max}} \) times blood \( O_2 \) capacity), \( FQ \), (2) capillary perfusion and diffusion, \( Fc \), and (3) mitochondrial capacity, \( Fm \)

<table>
<thead>
<tr>
<th>( \alpha )</th>
<th>( \dot{F}Q )</th>
<th>Two legs ( \dot{F}c )</th>
<th>( \dot{F}m )</th>
<th>One leg ( \dot{F}c )</th>
<th>( \dot{F}m )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>0.80</td>
<td>0.005</td>
<td>0.195</td>
<td>0.61</td>
<td>0.01</td>
</tr>
<tr>
<td>0.10</td>
<td>0.79</td>
<td>0.02</td>
<td>0.19</td>
<td>0.60</td>
<td>0.03</td>
</tr>
<tr>
<td>0.5</td>
<td>0.77</td>
<td>0.05</td>
<td>0.18</td>
<td>0.55</td>
<td>0.15</td>
</tr>
<tr>
<td>1.0</td>
<td>0.72</td>
<td>0.14</td>
<td>0.14</td>
<td>0.52</td>
<td>0.26</td>
</tr>
<tr>
<td>2.0</td>
<td>0.68</td>
<td>0.21</td>
<td>0.11</td>
<td>0.47</td>
<td>0.35</td>
</tr>
<tr>
<td>10</td>
<td>0.59</td>
<td>0.37</td>
<td>0.04</td>
<td>0.38</td>
<td>0.56</td>
</tr>
<tr>
<td>100</td>
<td>0.55</td>
<td>0.44</td>
<td>0.01</td>
<td>0.35</td>
<td>0.64</td>
</tr>
</tbody>
</table>

The three factors, \( FQ, Fc \) and \( Fm \), are expressed in relative units (\( FQ + Fc + Fm = 1.0 \)), and the two peripheral ones are assumed to be interdependent, being related by the coefficient \( \alpha \): \( Fc = \alpha Fm \). See text for details.
Fig. 2. Average changes (±s.d.) of $\dot{V}_{O_2}\text{max}$, SDH activity, capillary cross sectional area (CCA) and maximal cardiac output ($Q_{\text{max}}$) following two-legged endurance training. Number of observations in brackets. Data from Andersen & Henriksson (1977); Henriksson & Reitman (1976, 1977); Ekblom et al. (1968) and Saltin et al. (1968).

Fig. 3. Fractional limitations of $\dot{V}_{O_2}\text{max}$ due to $O_2$ transport (FQ), capillary perfusion and diffusion (Fc) and mitochondrial capacity (Fm) during two-legged maximal exercise, as a function of the coefficient $\alpha (= Fc/Fm)$, equation 14). (See text for details.)
and that the two peripheral limiting factors are interdependent,

\[ Fc = \alpha Fm, \]  

then, \( Fm, Fc \) and \( FQ \) can be calculated with the aid of equation 12 for any predetermined value of \( \alpha \) (Table 2, Fig. 3).

For low values of \( \alpha \), i.e. assuming that peripheral perfusion and diffusion do not limit \( \dot{V}_{O2}\max \) to any significant extent, about 80\% of \( \dot{V}_{O2}\max \) is set by \( O_2 \) transport, the remaining 20\% being due to mitochondrial capacity. On the contrary, if the assumption is made that the mitochondrial capacity does not set any limit to \( \dot{V}_{O2}\max \) (\( \alpha > 100 \)), about 55\% of \( \dot{V}_{O2}\max \) depends on \( O_2 \) transport, the remaining 45\% being due to peripheral diffusion and perfusion (Table 2, Fig. 3).

A reasonable solution to this dilemma is to assume that the two peripheral factors in question are equally effective in limiting \( \dot{V}_{O2}\max \). This amounts to saying that \( \alpha = 1 - 0 \), a value close to that calculated from the ratio of \( \Delta Rc/\Delta Rm = 0.64 \) (Fig. 2). If this is so, then \( FQ = 0.72 \) and \( Fc = Fm = 0.14 \) (Table 2). The obtained value of \( FQ \) is not far from that calculated from Fig. 1, thus supporting the hypothesis that \( \dot{V}_{O2}\max \) is limited chiefly by the \( O_2 \) transport to tissues.

The percentage increases of \( \dot{V}_{O2}\max \) and of mitochondrial enzyme activity during one-legged (cycling) exercise are indicated in Fig. 4, using the data of Henriksson.
(1977) and Saltin et al. (1976). No measurements were made under these conditions of capillary cross section and cardiac output changes. It can be assumed however that: (a) the former is the same as in two-legged training, and (b) the latter is equal to the \( \dot{V}_O_2 \) \(_{\text{max}} \) changes observed in the untrained leg in which no increase in enzymatic activity was observed (Henriksson, 1977; Saltin et al. 1976). If this is so (Fig. 4), and on the basis of the two assumptions outlined in equations 13 and 14, \( F_m \), \( F_c \) and \( F_Q \) can be calculated as a function of \( \alpha \) (Table 2). The general trend that emerges is similar to that observed in two-legged exercise; for all values of \( \alpha \), however, \( F_Q \) is smaller and \( F_c \) and \( F_m \) greater in one-legged (as compared to two-legged) exercise, thus indicating that \( O_2 \) transport is less crucial in setting \( \dot{V}_O_2 \) \(_{\text{max}} \) during exercise with small muscle groups. If, once again, the assumption is made that the two peripheral factors have equal weight \( (\alpha = 1.0) \), then \( F_Q = 0.52 \) and \( F_c = F_m = 0.26 \) (Table 2).

**DISCUSSION**

The above analysis and calculations depend on a series of assumptions that need to be explicitly stated and discussed.

1. Ventilation and pulmonary diffusing capacity for \( O_2 \) have not been considered among the possible factors limiting \( \dot{V}_O_2 \)\(_{\text{max}} \). This view seems well supported, at least for healthy subjects in normoxia (Shephard, 1971) and will not be further discussed.

2. The present approach can be meaningfully applied only if the overall pressure gradient from environment to mitochondria is not affected by the experimental manipulations affecting \( \dot{V}_O_2 \)\(_{\text{max}} \). For all conditions here considered (blood loss or infusion and training) a different assumption would indeed seem rather awkward, even if small changes of \( O_2 \) partial pressure at the peripheral end may in fact occur.

3. The three resistances \( R_Q \), \( R_c \) and \( R_m \) have been considered proportional to maximal \( O_2 \) transport capacity, capillary cross section and SDH activity (see equations 7—9). This simplification was introduced since the knowledge of the different morphological and physiological parameters that make up the various resistances (or conductances) is not detailed enough to warrant other approaches at present.

4. In Table 1, the changes of the resistance to \( O_2 \) transport \( (\Delta R_Q/R_Q) \) have been calculated (in seven out of 10 cases) from the \([Hb] \) changes, thus neglecting any eventual changes of \( Q_{\text{max}} \). When measured, these were found to be rather small (Ekblom et al. 1972; Woodson et al. 1978) and, if taken into account, they tend to reduce the calculated value of \( \Delta R_Q/R_Q \). This would therefore lead to an increase in the slope of the regression of Fig. 1, and hence to a greater value of \( F_Q \) which, in this case, may approach 0.90.

5. The peripheral limiting factors (diffusion and perfusion from capillary to cell, and \( O_2 \) utilization at the mitochondrial level) have been assumed to be interdependent (equation 14). The alternative assumption that the limitation due to peripheral perfusion and diffusion, \( F_c \), is proportional to that due to \( O_2 \).
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transport, $FQ$ ($F_c = \alpha F_Q$), leads to quite different results from those in Table 2. On this basis, in fact, during two-legged exercise $FQ$ is in the range 0.75–0.50 for small values of $\alpha$ ($\alpha < 1.0$), but decreases dramatically for $\alpha > 1.0$, to attain 0.12 for $\alpha = 10$. However, since the two sets of peripheral factors here considered are both affected by the same (presumably) local stimuli, it seems reasonable to assume that they are related to each other rather than to cardiac output. Hence the assumption that $F_c = \alpha F_m$ (equation 14).

(6) The fraction of $Q_{\text{max}}$ perfusing the working muscles has been implicitly assumed not to change with training. An eventual increase of this fraction with training would lead to values of $FQ$ smaller, and of $F_c$ and $F_m$ greater, than those reported in Table 2.

The above analysis, assumptions and calculations suggest that, during maximal whole body exercise, $V_{O_2}\text{max}$ is essentially limited by cardiac output, a conclusion that is shared by many authors although based on different grounds (e.g. Shephard, 1976; Saltin & Gollnick, 1983). Contrary to the above conclusions is the opinion of Ivy, Costill & Maxwell (1980) who assign a major role to muscle respiratory capacity in determining $V_{O_2}\text{max}$. These authors base their conclusion on the results of a statistical analysis on 20 physically active subjects which showed that 72% of the variance in $V_{O_2}\text{max}$ could be explained by the combined effects of muscle respiratory capacity and percentage of slow twitch (ST) fibres. However, since $Q_{\text{max}}$ was not measured, this type of analysis cannot show the fraction of the total $V_{O_2}\text{max}$ variability that depends on $Q_{\text{max}}$. In addition, this type of statistical analysis cannot, in my opinion, be used to infer causal relationships between the investigated parameters. The relatively minor importance of the periphery as a limiting factor is also consistent with the data of Gollnick et al. (1973) who observed an average increase of $V_{O_2}\text{max}$ by 13% after 5 months' endurance training in humans ($N = 6$) while mitochondrial SDH activity increased on average by 95%, i.e. to a much larger extent than reported in Fig. 2.

It must also be pointed out that the fractions of the $V_{O_2}\text{max}$ limitation obtained from the training data were calculated assuming that $AR_m$ is proportional to the change of succinate dehydrogenase activity rather than from the increase of the overall mitochondrial capacity in vitro. The latter increases by 50–100% both in man (Holloszy et al. 1977) and in rats (Patch & Brooks, 1980), i.e. to a larger extent than the former (~30%) (Figs 2, 4). On the basis of these data, therefore, the importance of mitochondria as a limiting factor would become smaller, and that of $O_2$ transport larger, than reported in Table 2.

During one-legged exercise the fraction of $V_{O_2}\text{max}$ limitation due to the periphery seems to become more important, although the general picture remains substantially unchanged (Table 2).

It becomes immediately apparent that the type of analysis presented above can, in principle, be extended to other situations of which the following seem to be of some interest. (1) Animals of different size, in which case the relative importance of the various limiting factors may be different from that in man and, eventually, size dependent. (2) Different types of training in man, in which case the adaptations of $Q_{\text{max}}$, capillary cross section and muscle enzymatic activity may change from one
type of training to another. This may allow the use of a system of three (or more) experimental equations with three unknowns (equation 6), thus eliminating the need for the coefficient $\alpha$ (equation 14). (3) High altitude acclimation in man, in which case $\dot{V}_O_{\text{max}}$, $Q_{\text{max}}$, [Hb], capillary cross section and muscle enzymatic activity are known to change (Cerretelli, Marconi, Dériaz & Giezendanner, 1984; Boutellier et al. 1983). This may allow study of the behaviour of the various factors limiting $\dot{V}_O_{\text{max}}$ in the course of the acclimation period. At present, there is insufficient data for a detailed analysis of these three situations.

In concluding, I would like to point out that the results of the above analysis should be viewed with care in the light of the many assumptions and approximations involved in the calculations. They do support the view, however, that whole body $\dot{V}_O_{\text{max}}$ is mostly (~80%) limited by cardiac output, while for exercises with small muscle groups the role of the periphery becomes more important, attaining about 50% during one-legged maximal exercise.

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REFERENCES


Limitations to oxygen consumption


