On maximal oxygen consumption in hypoxic humans

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Summary. The present paper discusses the factors affecting maximal O_2 consumption ($\dot{V}_{O_2}max$) in hypoxia (4300 m above sea level) along the following lines: 1) In acute hypoxia, the fractional limitation to $\dot{V}_{O_2}max$ imposed by circulatory O_2 transport (FQ') is 50%, instead of 70% as in normoxia. This is due to the increase in the blood O_2 transport coefficient (βb) as P_{O_2} decreases, as a consequence of the sigmoidal shape of the O_2 dissociation curve of hemoglobin. The remaining 50% is assumed to be equally partitioned between tissue O_2 transfer (Ft') and mitochondria O_2 utilization (Fm'). 2) In chronic hypoxia, FQ' = 0.45, Ft' = 0.20 and Fm' = 0.35, as a consequence of reduced muscle fiber size and muscle mitochondrial density following acclimatization. 3) The relationship between $\dot{V}_{O_2}max$ and PI_{O_2} in both acute and chronic hypoxia reflects the O_2 dissociation curve. 4) Acclimatization to chronic hypoxia does not have the function of preserving $\dot{V}_{O_2}max$.

Key words. Maximal O_2 consumption; acute and chronic hypoxia; maximal cardiac output; hemoglobin; O_2 dissociation curve; muscle morphometry; limiting factors.

Introduction

When the inspired O_2 tension (PI_{O_2}) is reduced, both acutely and chronically, the maximal aerobic power (maximal O_2 consumption, $\dot{V}_{O_2}max$) decreases, following a curve whose slope becomes steeper as PI_{O_2} drops (fig. 1). The same holds true when PI_{O_2} is replaced by arterial O_2 pressure, Pa_{O_2} [4]. The shape of the curve in figure 1 has intrigued several physiologists [1, 4, 31, 33]. Two main questions arise from figure 1: 1) which are the factors limiting $\dot{V}_{O_2}max$ in hypoxia? and 2) what is the meaning of the curve relating $\dot{V}_{O_2}max$ to PI_{O_2}? The present paper is an attempt to answer these questions.

The concept of limiting factor

Before discussing the factors limiting $\dot{V}_{O_2}max$ in hypoxia, let us briefly define what is meant by limiting factor. Let A and B be two parameters with (maximal) values a and b, respectively. B is a limiting factor of A if and only if: 1) induced or adaptive relative changes in b cause equal or lower relative changes in a; 2) the relationship between B and A is univocal. When all other factors affecting A stay or can be assumed to remain constant, and if the system in question behaves linearly, the size of the limits to A imposed by B (FB) is given by:

$$FB = \left(\frac{a}{a + \Delta a} - 1\right) \cdot \frac{b}{\Delta b} \qquad (1)$$

FB ranging from 0 to 1. If B is the only factor limiting A, FB = 1. If A is limited by more than one factor (B + 1, B + 2, ..., B + n), then FB < 1 and FB + (FB + 1) + (FB + 2) + ... + (FB + n) = 1.

$\dot{V}_{O_2}max$ is usually stated to be limited (exclusively or mostly) by one single factor, i.e. by convective O_2 transport (maximal cardiac output times maximum O_2 binding capacity of hemoglobin [8, 24]. However, several other parameters have been called upon as possible factors limiting $\dot{V}_{O_2}max$ in humans, such as the overall mitochondrial oxidative capacity, the muscle capillary density [N_A(c, f)], or some other parameter related to muscle O_2 transfer, maximum muscle blood flow, and alveolar ventilation at maximal exercise. Thus, in order to analyze the factors limiting $\dot{V}_{O_2}max$, a quantitative multifactorial approach is most desirable.

A multifactorial model of the factors limiting $\dot{V}_{O_2}max$ has been recently proposed, the mathematical description of which can be found elsewhere [6, 7]. The model is a simpli-

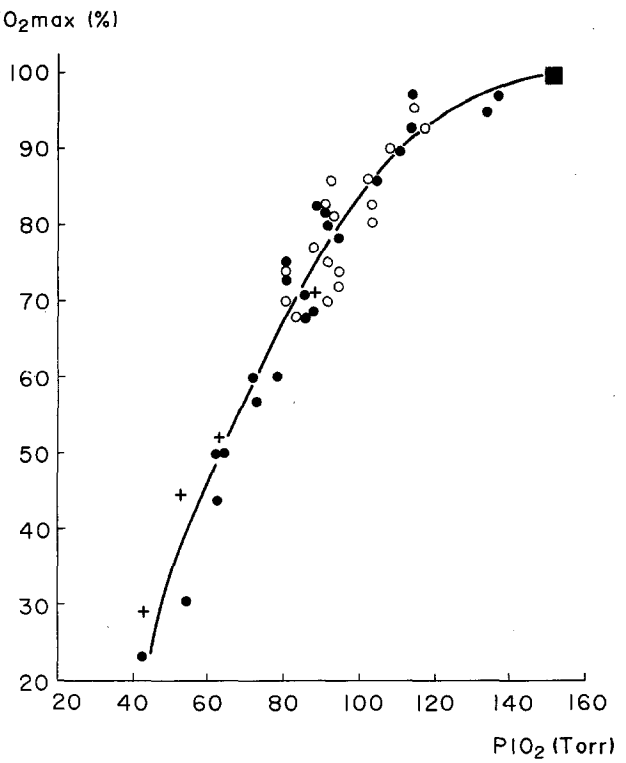

Figure 1. Relative values of maximal O_2 consumption ($\dot{V}_{O_2}max$) (reference value at sea level equal to 100%) as a function of PI_{O_2}. ●, chronic hypoxia; ○, acute hypoxia; +, Operation Everest II; ■, reference at sea level. Data from Refs 3, 4, 5, 9, 13, 14, 15, 20, 25, 28, 35.

List of symbols or abbreviations used in the text

Symbol	Definition	Unit
Ca_{O_2}	O_2 concentration in arterial blood	ml/l
$(Ca-C\bar{v})_{O_2}$	Arterio-venous difference for O_2 concentration	ml/l
$C\bar{v}_{O_2}$	O_2 concentration in mixed venous blood	ml/l
Fm′	Fractional limitation of maximal O_2 consumption due to mitochondria oxidative capacity	unitless
FQ′	Fractional limitation of maximal O_2 consumption due to circulatory O_2 transport	unitless
Ft′	Fractional limitation of maximal O_2 consumption due to tissue O_2transfer	unitless
G	Conductance to O_2 flow (reciprocal of resistance)	l/min · Torr
Hb	Hemoglobin concentration	g/l
$N_A(c,f)$	Number of capillaries per unit area of muscle fiber, or muscle capillary density	mm^{-2}
O_2ext	O_2 extraction from arterial blood at the capillary level. Equal to $\dot{V}_{O_2}max/\dot{Q}_{O_2}$ and to $(Ca\text{-}C\bar{v})_{O_2}/Ca_{O_2}$	unitless
PA_{O_2}	Alveolar air O_2 partial pressure	Torr
Pa_{O_2}	Arterial blood O_2 partial pressure	Torr
$(Pa-P\bar{v})_{O_2}$	Arterio-venous O_2 pressure gradient	Torr
$P\bar{c}_{O_2}$	Average capillary O_2 partial pressure	Torr
PI_{O_2}	Inspired air O_2 partial pressure	Torr
$P\bar{v}_{O_2}$	Mixed venous blood O_2 partial pressure	Torr
$\dot{Q}$	Cardiac output	l/min
$\dot{Q}max$	Maximal cardiac output	l/min
$\dot{Q}_{O_2}$	O_2 flow in arterial blood at maximal exercise	l/min
Rm	Resistance to O_2 flow imposed by oxidative capacity of mitochondria	Torr · min/l
RQ	Resistance to O_2 flow imposed by circulatory O_2 transport	Torr · min/l
Rt	Resistance to O_2 flow imposed by tissue O_2 transfer	Torr · min/l
RT′	Overall resistance to O_2 flow in the respiratory system downstream the lung $RT' = RQ + Rp + Rm$	Torr · min/l
Sa_{O_2}	O_2 saturation of hemoglobin	unitless
$\dot{V}A$	Alveolar ventilation	l/min
$\dot{V}_{O_2}max$	Maximal O_2 consumption	l/min
$V_v(mt,f)$	Volume density of muscle mitochondria, i.e. the volume of mitochondria per unit volume of muscle fiber	%
βO_2	O_2 transport coefficient of hemoglobin. This corresponds to the average slope of the O_2 dissociation curve for hemoglobin: $\beta O_2 = (Ca-C\bar{v})_{O_2}/(Pa-P\bar{v})_{O_2}$	Torr · min/l

fied application of the O_2 conductance equation [26, 27, 29] downstream of the lungs. Within this framework, O_2, driven by a pressure gradient, is assumed to flow from the alveoli to the mitochondria against a number of resistances in series. These resistances have been combined by di Prampero [6] into three main resistances of specific physiological meaning: the first (RQ) is related to blood convective O_2 transport, and it is inversely proportional to the maximal cardiac output ($\dot{Q}max$) times the O_2 transport coefficient, βb (average slope of the O_2 dissociation curve); the second (Rt) is related to peripheral O_2 transfer, and probably depends on $N_A(c,f)$; the third (Rm) is related to the overall capacity of mitochondria to consume O_2 and is set proportional to the volume density of muscle mitochondria ($V_V(mt,f)$). The total resistance to O_2 flow (RT′) is given by the sum of the above three resistances. For any given P_{O_2}, the role of each factor (FQ′, Ft′, Fm′) in limiting $\dot{V}_{O_2}max$ results from the interplay of RQ, Rt and Rm, so that $FQ' = RQ/RT'$, $Ft' = Rt/RT'$ and $Fm' = RmRT'$.

In untrained humans in normoxia, FQ′ was found to be 0.7, and thus $Ft' + Fm' = 0.3$. Ft′ and Fm′ cannot be obtained independently. It was thus arbitrarily assumed that $Ft' = Fm' = 0.15$. In subjects who had become acclimatized to hypoxia, upon their return to sea level (acute normoxia), FQ′, Ft′ and Fm′ were recalculated starting from the conclusions arrived at for normoxic subjects. Compared to normoxia, the results appeared to differ very little: in fact, FQ′ was = 0.7, Ft′ 0.1 and Fm′ 0.2 [7].

A discussion of some assumptions and limits of the model applied in the present study is given elsewhere [7]. It is noteworthy, however, that the driving O_2 pressure at the peripheral capillaries is not the average capillary pressure ($P\bar{c}_{O_2}$), that is used to calculate the O_2 diffusion capacity, but $P\bar{v}_{O_2}$. Similarly, at the lung level, the driving pressure is Pa_{O_2} instead of $P\bar{c}_{O_2}$, so that the pressure gradient driving circulatory O_2 transfer is $Pa_{O_2} - P\bar{v}_{O_2}$ and not $P\bar{c}_{O_2} - P\bar{c}_{O_2} =$ zero. The latter, in fact, would lead to $RQ = 0$ and to a product $\beta O_2 \cdot \dot{Q} = \infty$, which not only is incompatible with a resistance-like model of O_2 flow, but also has no physiological meaning.

Factors limiting $\dot{V}_{O_2}max$ in hypoxia

The multifactorial model of the factors limiting $\dot{V}_{O_2}max$ briefly presented above is a particular case of a possible general model. In fact, in the above scheme, the following conditions are imposed: 1) The overall pressure difference, ΔP, is set constant and equal to sea level Pa_{O_2}; 2) The average slope (βb) of the O_2 dissociation curve is therefore not allowed to vary, so that it can be neglected in the definition of the parameter(s) proportional to RQ; 3) The percent amount of cardiac output directed to the muscles at maximal exercise level is constant (75–80% [23]; 4) Alveolar ventilation and alveolar-arterial O_2 diffusion do not limit $\dot{V}_{O_2}max$ at sea level, because any increase of these two factors cannot enhance the O_2 content of arterial blood: indeed, the flatness of the O_2 dissociation curve around sea level Pa_{O_2} values implies that any possible increase in Pa_{O_2} is offset by an equal and opposite change in βb [7].

It is evident that, among the above-cited conditions imposed on the model, only condition 3) can apply to chronic hypoxia. Conditions 1) and 2) are definitely not

valid. Condition 4) is certainly not applicable on top of Mount Everest, where Pa_{O_2} and Ca_{O_2} lie on the steep linear segment of the O_2 dissociation curve, and it is perhaps doubtful at lower altitudes, where Pa_{O_2} and Ca_{O_2} lie on the bend of the O_2 dissociation curve (see below for a further discussion of this topic). An estimate of the factors limiting $\dot{V}_{O_2}max$ in hypoxia can thus be attempted by either formulating the systems of equations of a general model in which the 4 conditions imposed by di Prampero [6] are allowed to vary, or by applying a step-by-step procedure, in which the variables affected by chronic hypoxia change separately and at different times. The latter procedure will be pursued in the next paragraphs along the following lines: 1) move from normoxia to acute hypoxia by reducing PI_{O_2}; 2) let hypoxia become chronic without changing PI_{O_2}.

Acute hypoxia

In acute hypoxia, it is likely that no changes in $V_V(mt, f)$ and in $N_A(c, f)$ occur. Thus, assuming that Rt and Rm remain constant, one deals with changes in RQ only, that is to say with changes in the product of $\dot{Q}max$ times βb. For the sake of simplicity, however, since in the conditions considered O_2 extraction does not appear to be different from that in normoxia, RQ is set proportional to the O_2 flow in arterial blood, $\dot{Q}_{O_2}$ ($= \dot{Q}max \cdot Ca_{O_2}$, this last being arterial blood O_2 concentration). The evolution of the hematologic and hemodynamic variables affecting $\dot{Q}_{O_2}$ in subjects acutely exposed to hypoxia is described in table 1.

It can be calculated from table 1 that in normoxia RT′ is equal to 96/3.04 = 31.58 R.U. (Torr · min · l^{-1}). Assuming FQ′ = 0.7 and Ft′ + Fm′ = 0.3, RQ = 0.7 RT′ = 22.11 R.U., and Rt + Rm = 0.3 RT′ = 9.47 R.U. In hypoxia (4300 m a.s.l.), in spite of the invariance of Rt + Rm, RT′ drops markedly (RT′ = 42/2.32 = 18.10 R.U., i.e. 43% less than in normoxia). The calculated reduction in RT′ must result from a corresponding decrease in RQ: RQ = RT′ − Rt − Rm = 18.10 − 9.47 = 8.63 R.U. If this is so, then FQ′ = 8.63/18.10 = 0.48 instead of 0.70.

What are the reasons for the calculated reduction in FQ′ in hypoxia? The general equation describing the net O_2 flow through the circulatory portion of the O_2 pathway is [29]:

$$\dot{V}_{O_2} = (Pa - P\bar{v})_{O_2} \cdot G \qquad (2)$$

where G is the conductance term (reciprocal of resistance), equal to the product of maximal cardiac output, $\dot{Q}max$, times the average slope of the O_2 dissociation curve, βb. Due to the non linear shape of this curve, as Pa_{O_2} decreases (hypoxia), βb increases until Pa_{O_2} lies on the steep part of the curve. This leads to a higher G (lower resistance) in Eq. 2, and thus to higher $\dot{Q}_{O_2}$ and $\dot{V}_{O_2}max$ values than predicted on the basis of a reduction in the O_2 pressure gradient only. It is therefore justified to conclude that the fractional limitation of $\dot{V}_{O_2}max$ imposed by convective blood O_2 transport (RQ) is smaller in hypoxia because of the intrinsic characteristics of the O_2 dissociation curve. The theoretical variations of FQ′ as Pa_{O_2} is decreased are shown in figure 2.

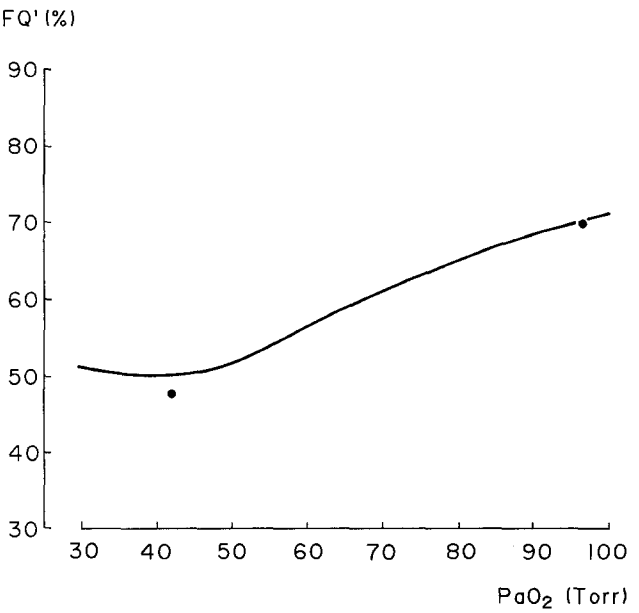

Figure 2. Fractional limitations to $\dot{V}_{O_2}max$ imposed by circulatory O_2 transport (FQ′) as a function of acutely decreased Pa_{O_2}. The line is theoretical, and has been calculated on the assumption that in acute hypoxia, 1) $\dot{Q}max$ is unchanged (according to fig. 3, this assumption is certainly false in extreme hypoxia); 2) Rt = Rm = constant; and thus 3) changes in the O_2 pressure gradient are accompanied by changes in the average slope of the O_2 dissociation curve, βb, only. Dots are estimates from experimental data, as described in the text.

Table 1. Cardiovascular and hematologic parameters in acute hypoxia

	n	Alt. (m)	$\dot{V}_{O_2}max$ (l/min)	$\dot{Q}max$ (l/min)	$(Ca-C\bar{v}_{O_2})$ (ml/l)	Hb (g/l)	Sa_{O_2} (%)	Ca_{O_2} (ml/l)	$\dot{Q}_{O_2}$ (l/min)	O_2ext (%)	Pa_{O_2} (Torr)
Hansen et al. [13]	8	0	2.53	13.8	184	169	96	218	3.01	84	107
		4300	2.18	15.6	140	183	77	189	2.95	74	45
Hartley et al. [15]	7	0	2.81	17.5	161	161	100	216	3.78	74	91
		4300	2.12	17.0	125	155	77	160	2.72	78	40
Saltin et al. [25]	4	0	3.81	22.0	173	153	95*	195*	4.29*	89	89
		4300	2.66	19.0	134	153	77*	158*	3.00	89	45
Stenberg et al. [28]	6	0	3.46	23.7	146	142	94	179	4.24	82	90*
		4300	2.50	23.2	108	141	70	132	3.06	82	40*
X	25	0	3.04	18.5	167	158	96	204	3.77	81	96
		4300	2.32	18.5	127	160	75	162	3.00	77	42

Data labeled with an asterisk are estimates.

Chronic hypoxia

Acclimatization to hypoxia occurs in both the cardiovascular system and the muscles, leading probably to changes in all three of the resistances to O_2 flow that are considered. However, only very sparse data, obtained for conditions of chronic hypoxia, exist for the parameters related to such resistances, with the single exception of Hb. $\dot{Q}$max was determined by Saltin et al.[15] after 2 weeks at 4300 m and was found to be 7% lower than in acute hypoxia at the same PI_{O_2} (see table 2). With respect to control values in normoxia, Pugh[19] found a decrease in $\dot{Q}$max after 3 months at 5800 m from 23.7 to 16.8 l/min (−29%), which was accompanied by a 39.5% decrease in peak $\dot{V}_{O_2}$. Conversely, Operation Everest II[22] showed at 6100 m a decrease in $\dot{Q}$max by only 6% compared to sea level controls. However, the subjects of the last-cited study were probably not fully acclimatized[34]. V_V(mt, f) and N_A(c, f) were determined on a group of subjects participating in the 1986 Swiss expedition to Mt. Everest[16]: the results of this study are also summarized in table 2.

In Saltin et al.'s[25] subjects in acute hypoxia, Pa_{O_2} was 45 Torr, and thus RT′ was 45/2.66 = 16.92 R.U. For FQ′ = 0.48, and assuming Ft′ = Fm′ = (1−0.48)/2 = 0.26, we obtain RQ = 8.12 R.U., and Rt = Rm = 4.40 R.U. In chronic hypoxia (table 2), the increase in Ca_{O_2}, due to the higher hemoglobin concentration, more than compensated for the drop in $\dot{Q}$max, so that a $\dot{Q}_{O_2}$ value resulted which was 4% higher than in acute hypoxia. Thus, RQ = 8.12/1.04 = 7.81 R.U. By the same token, RT = 4.40/1.28 = 3.44 R.U., and Rm = 4.40/0.74 = 5.95 R.U., so that RT′ = RQ + Rt + Rm = 17.20 R.U., which is practically equal to the value found in acute hypoxia. Similarly, $\dot{V}_{O_2}$max was practically unchanged, being 2.61 l/min instead of 2.66 l/min. In spite of this, however, the fractional limitation to $\dot{V}_{O_2}$max varies: FQ′ = 7.81/17.20 = 0.45; Ft′ = 3.44/17.20 = 0.20; and Fm′ = 5.95/17.20 = 0.35. The two peripheral factors become dissociated, as the role of Fm′ increases and that of Ft′ decreases. However, the overall peripheral fraction of $\dot{V}_{O_2}$max limitation, i.e. the sum of Ft′ plus Fm′, remains unchanged, so that FQ′ comes out equal in acute and chronic hypoxia at the same P_{O_2}. Similar conclusions were drawn after experiments in acute normoxia[7].

Adaptation to hypoxia takes place in such a way that the relative changes in the parameters affecting $\dot{V}_{O_2}$max compensate each other, so that the reduced $\dot{V}_{O_2}$max values do not vary in the course of acclimatization. The reduced mitochondrial density counterbalances the increased capillary density, whereas the increase in Hb, and hence in Ca_{O_2} is offset by a corresponding change in $\dot{Q}$max. Nevertheless, also in adapted subjects, FQ′ was lower at altitude (chronic hypoxia) than upon return to sea level (acute normoxia). Again, this may be attributed to the shape of the O_2 dissociation curve, allowing preservation of relatively high Ca_{O_2} values in spite of great drops in Pa_{O_2}.

Table 2. Factors determining $\dot{V}_{O_2}$max in acute and chronic hypoxia

		Acute	Chronic	%	
$\dot{V}_{O_2}$max	(l/min)	2.66	2.61	− 1.9	
$\dot{Q}$max	(l/min)	19.0	17.7	− 6.9	
Hb	(g/l)	153	171		Saltin et al.[25]
Ca_{O_2}	(ml/l)	158	176	+ 11.4	
Sa_{O_2}	(%)	77	77	0.0	
$\dot{Q}_{O_2}$	(l/min)	3.00	3.12	+ 4.0	
V_V(mt, f)	(%)	5.02	4.12	− 26.0	Hoppeler et al.[16]
N_A(c, f)	(mm^{-2})	468	599	+ 28.0	

The analysis of FQ′, Ft′ and Fm′ conducted in this paragraph assumes that alveolar ventilation ($\dot{V}$A) plays no role as a factor limiting $\dot{V}_{O_2}$max. This may well be true at sea level, when Pa_{O_2} lies on the flat part of the O_2 dissociation curve. In fact, an increase in $\dot{V}$A, which reduces the resistance to O_2 flow at the level of the lungs, thus increasing Pa_{O_2} is necessarily accompanied by a decrease in βb, which enhances RQ. Since the changes in the two resistances considered are equal in size but of opposite sign, it follows that changes in $\dot{V}$A at sea level do not lead to any changes in $\dot{V}_{O_2}$max[7]. At altitude, however, when Pa_{O_2} lies on the steep part of the O_2 dissociation curve, hyperventilation helps to prevent Ca_{O_2} from falling, so that also $\dot{V}$A may limit $\dot{V}_{O_2}$max. Indeed, spontaneous hyperventilation has been shown by some authors[21, 34] to occur in subjects adapted to altitude, and the subjects included in the present analysis also seemed to hyperventilate when acclimatized. However, they showed PA_{O_2} and Sa_{O_2} values in chronic hypoxia equal to those in acute hypoxia (table 2) when they did not hyperventilate. It seems, therefore, that hyperventilation in chronic hypoxia did not affect the circulatory side of the O_2 transport system, at least in Saltin et al.'s[25] subjects at 4300 m. On this basis, we deem it to be justifiable to neglect $\dot{V}$A as a factor limiting $\dot{V}_{O_2}$max in the experimental condition considered.

The $\dot{V}_{O_2}$max versus PI_{O_2} relationship

The conclusions arrived at in the chapter on the acute hypoxia experiments lead to the hypothesis that the curve relating $\dot{V}_{O_2}$max to P_{O_2} (fig. 1) reflects the O_2 dissociation curve. The present chapter is aimed at supporting this hypothesis.

According to the Fick's equation:

$$\dot{V}_{O_2}\text{max} = \dot{Q}\text{max} \cdot (Ca - C\bar{v})_{O_2} \quad (3)$$

Since:

$$O_2\text{ext} = \frac{Ca_{O_2} - C\bar{v}_{O_2}}{Ca_{O_2}} \quad (4)$$

where O_2ext is O_2 extraction from the capillaries, equation (3) can also be written as follows:

$$\dot{V}_{O_2}\text{max} = \dot{Q}\text{max} \cdot Ca_{O_2} \cdot O_2\text{ext} \quad (5)$$

O_2ext at maximal exercise in normoxia ranges between 0.80 and 0.85, and it does not vary in acute hypoxia[28]. Ca_{O_2} in turn is equal to:

$$Ca_{O_2} = 1.34 \cdot Sa_{O_2} \cdot Hb \quad (6)$$

where Hb is blood hemoglobin (in g/l), and Sa_{O_2} is arterial O_2 saturation (unitless). Since Ca_{O_2} is in ml_{O_2}/l, the constant 1.34, indicating the O_2 affinity of normal hemoglobin, is expressed in ml_{O_2} per g of hemoglobin. A combination of Eqs 5 and 6 yields:

$$\dot{V}_{O_2}max = \dot{Q}max \cdot 1.34 \cdot Sa_{O_2} \cdot Hb \cdot O_2ext \quad (7)$$

Assuming constant Hb, and grouping all constants, we obtain:

$$\dot{V}_{O_2}max = K \cdot Sa_{O_2} \cdot \dot{Q}max \quad (8)$$

where K is in ml_{O_2}/l. Equation (8) implies that, when $\dot{V}_{O_2}max$ is plotted as a function of $\dot{Q}max$, experimental points lie on Sa_{O_2} isopleths, that are related to $(Ca-C\bar{v})_{O_2}$ by the constant K. Another consequence of Eq. 8 is that $\dot{V}_{O_2}max$ is linearly related to Sa_{O_2} in a plot where isopleths radiating from the origin are proportional to $\dot{Q}max$ (fig. 3). Figure 3 shows that, in acute hypoxia, one should expect a slight increase in $\dot{Q}max$. More data at various PI_{O_2} levels are required, however, to confirm this prediction.

The above analysis shows that, since $\dot{V}_{O_2}max$ is proportional to Sa_{O_2} and Sa_{O_2} is related to Pa_{O_2} (O_2 dissociation curve), and thus to PI_{O_2}, for the transitive property $\dot{V}_{O_2}max$ must be related to Pa_{O_2} and/or PI_{O_2} (fig. 1). The shape of the line in figure 1 is curvilinear because the O_2 dissociation curve is curvilinear. Indeed, to put $\dot{V}_{O_2}max$ or Sa_{O_2} on the ordinate of figure 1 is equivalent.

When chronic hypoxia is also taken into account, one finds that the data obtained after altitude acclimatization lie, on the $\dot{V}_{O_2}max$ vs P_{O_2} plot, on the same line as those obtained in acute hypoxia (fig. 1). This finding has been defined as paradoxical[4], since one would expect that the physiological changes induced by the acclimatization process have the function of preserving maximal O_2 flow. However, figure 1 has, in our opinion, a different meaning.

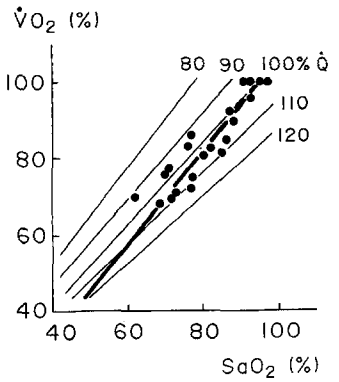

Figure 3. Relative $\dot{V}_{O_2}max$ as a function of arterial O_2 saturation, Sa_{O_2} in acute hypoxia. Thin lines indicate isopleths for relative maximal cardiac output. Least square regression through the points (thick line) yields the equation $\dot{V}_{O_2}max = -16.62 + 1.23\ Sa_{O_2}$, r = 0.92, n = 21. Sea level values are the 100% reference.

In the first place, figure 1 shows that also after acclimatization the $\dot{V}_{O_2}max$ vs P_{O_2} plot reflects the O_2 dissociation curve. Indeed, the acclimatization process does not influence O_2 transport and O_2 extraction; in fact, as reported above, the increase in Hb and in hematocrit in chronic hypoxia is counterbalanced by a decrease in $\dot{Q}max$. In addition, RQ does not change in chronic hypoxia, implying that the overall resistance to O_2 flow between the capillaries and the mitochondria (Rt + Rm), which imposes O_2 extraction, is also unchanged.

Secondly, figure 1 indicates that the function of the acclimatization process is not to oppose a reduction in $\dot{V}_{O_2}max$. What, then, is the meaning of altitude acclimatization? The question is controversial, and several hypotheses may be put forward. The decreased mitochondrial density may be interpreted in the light of the theory of symmorphosis[16, 28, 32]: as the maximal O_2 flow decreases, the structure consuming O_2 becomes "excessive", and therefore it is reduced in size. However, what the stimuli responsible for such structural changes are, is at present completely unknown. The increased capillary density is merely a result of muscle fiber shrinkage[16] due to a reduced muscle mass and a loss of muscle proteins[2, 11]. Actually, the total capillary length remains unchanged.

More difficult is an interpretation of the changes occurring in the O_2 transport system. It is known, however, that the relationship between cardiac output ($\dot{Q}$) and $\dot{V}_{O_2}$ is shifted upwards in acute hypoxia[15, 17, 25, 28, 30] and downwards in acute normoxia (acclimatized subjects shortly after return to sea level[10]). Since Ca_{O_2} is reduced in acute hypoxia and is increased in acute normoxia, it is suggested that, at any given work load (including maximal exercise) a negative linear relationship exists between $\dot{Q}$ and Ca_{O_2}[10]. This relationship is such that an imposed decrease in Ca_{O_2} is offset by an equivalent increase in $\dot{Q}$, so that the convective O_2 flow, $\dot{Q}_{O_2}$, remains constant (fig. 4). These observations lead to the hypothesis that $\dot{Q}_{O_2}$, rather than $\dot{Q}$, is regulated by some feedback mechanism. In this context, $\dot{Q}$ may represent the variable responsive to feedback, tuned by combined vagal and sympathetic activity, whereas Ca_{O_2} may constitute the input signal. If this is so, 1) the slope of the $\dot{Q}$ vs Ca_{O_2} relationship in figure 4 (93 ml/min per ml/l) is the gain of the feedback system; and 2) the carotid body and/or the aortic chemoreceptors may be viewed as the sensor organ[12, 18].

In the light of the above hypothesis, the increase in Hb in chronic hypoxia may be viewed as a long-term adaptation to the reduction in Ca_{O_2} occurring in hypoxia, which tends to reduce $\dot{Q}_{O_2}$. Higher Hb increases Ca_{O_2}, thus

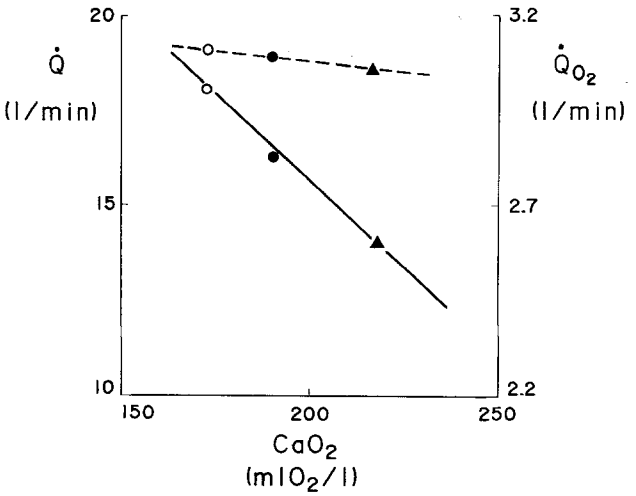

Figure 4. Cardiac output ($\dot{Q}$, left ordinate, continuous line) and O_2 flow ($\dot{Q}_{O_2}$, right ordinate, dashed line) as a function of Ca_{O_2}, at a work rate of 140 W. ○, acute hypoxia[28]; ●, normoxia[10]; ▲, acute normoxia[10]. From Ferretti et al.[10], with permission.

enhancing $\dot{Q}_{O_2}$. As a consequence, at any given work load, $\dot{Q}$, higher in acute hypoxia that in normoxia, drops towards the normoxic $\dot{Q}$ vs $\dot{V}_{O_2}$ line, thus reducing the work of the heart. And indeed, although this is "paradoxical"[31], the relationship between $\dot{Q}$ and $\dot{V}_{O_2}$ in chronic hypoxia is equal to that in normoxia[3, 19, 22], and $\dot{Q}$max in chronic hypoxia is lower than $\dot{Q}$max in acute hypoxia of the same intensity.

General conclusions

The results arrived at in the above analysis of the factors limiting $\dot{V}_{O_2}$max in hypoxic humans are summarized in table 3. Both in acute and in chronic hypoxia, the main role is played by circulatory O_2 transport. However, its role in hypoxia is less than in normoxia. This seems to be a consequence of the shape of the O_2 dissociation curve, which eases O_2 flow in hypoxia. After this analysis, the following conclusions have been drawn: 1) the non-linear decrease in $\dot{V}_{O_2}$max in both acute and chronic hypoxia is a mirror image of the O_2 dissociation curve; and 2) adaptation to hypoxia does not have the function of preserving $\dot{V}_{O_2}$max: it is rather the result of independent adaptive changes of different meanings and even opposite directions.

Table 3. Fractional limitation to $\dot{V}_{O_2}$max downstream from the lung

	FQ′	Ft′	Fm′
Normoxia	0.70	0.15	0.15
Acute hypoxia	0.48	0.26	0.26
Chronic hypoxia	0.45	0.20	0.35
Acute normoxia	0.70	0.11	0.19

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Control of respiration in skeletal muscle at rest

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Summary. The suggestion is made that, under resting conditions in situ, muscle cell respiration is dependent on the way O_2 and substrates are distributed to the cells by the microcirculation. (Delivery is measured as arterial-blood concentration multiplied by flow to the organ.) Microscale heterogeneity of this distribution, which is more marked but less stable than the more easily demonstrated larger-scale heterogeneity (0.1 to 0.5-g sampling grain), might indeed ration O_2 and substrates in a large population of the cells of a resting organ at any given moment, and microscale heterogeneity of distribution may thus take part in the normal control of cell respiration.
Key words. Skeletal muscle; cell respiration; maintenance metabolic rate; microcirculation; functional heterogeneity.

Introduction

I wish to draw attention to a *physiological* mechanism involving hypoxia in resting muscle. Limited transfer of oxygen or, more generally, limited transfer of substrates and products of oxidative metabolism between muscle cells and arterial blood perfusing the organ can be considered to be an integral component of respiratory control, and it is perhaps that component which allows muscle tissue maintenance at a low energy cost in the animal at rest. Any attempt to consider such an unorthodox viewpoint on respiratory control will meet with two major obstacles. First, the word hypoxia carries with it the idea that, somewhere, a *less-than-normal* amount of oxygen is available; second, feed-back matching of organ blood flow to organ metabolism is usually considered to occur at all aerobic metabolic rates, and this seems to imply a feed-back matching of capillary blood flow to cell metabolism at rest as well as in other aerobic steady-states.

Microscale heterogeneities in muscle

Using intravital microscopy and blood microsampling techniques, Duling and collaborators[4,6] have accumulated and confirmed direct evidence that feed-back matching of capillary O_2 availability to cell metabolism may not occur in skeletal muscle at rest. They observe a very significant heterogeneity of hemoglobin distribution to (and within) capillaries, and an equally marked microscale heterogeneity of blood flow distribution. The consequent heterogeneity of distribution of O_2 and substrate delivery to cells could limit the oxidative metabolism of a large population of cells in the organ at any given moment. The overall consequence would be a limitation of respiration in the muscle as a whole, despite non-limiting rates of delivery of O_2 and substrates to the organ. It has also been observed that constriction of the transverse arterioles leaving the muscle to enter the connective tissue may lead to a reduction of the local hematocrit (through accelerated movement of erythrocytes with respect to plasma) and the consequent diversion of red cells out of the muscle[14]. This particular kind of heterogeneity, however, does not seem to be the main cause of functional red-cell shunting in resting muscle.

Muscle oxygen consumption as a function of O_2 delivery

From the earliest to the most recent studies of the rate of muscle oxygen uptake ($\dot{M}_{O_2}$) as a function of the rate of oxygen transport to the organ ($\dot{T}_{O_2}$, which is the product of perfusate O_2 concentration and flow rate), two types of relationship have been observed. Some muscle preparations show *'O_2 conformity'*, that is, they *monotonously decrease* their $\dot{M}_{O_2}$ as $\dot{T}_{O_2}$ is decreased from a high value, by reducing either flow[7] or O_2 concentration[10]. Other preparations show *'O_2 regulation'*, that is, as $\dot{T}_{O_2}$ is reduced from a high value they *keep $\dot{M}_{O_2}$ constant* until a critically low $\dot{T}_{O_2}$ value is reached, a phenomenon that was described more than twenty years ago by Stainsby and Otis[6]. Since then it has usually been assumed that