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Factors limiting maximal O_2 consumption: effects of acute changes in ventilation

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Abstract

The response of the O_2 transport system to acute changes in alveolar ventilation ($\dot{V}A$) was analysed. The fractional limitations to maximal O_2 consumption ($\dot{V}_{O_2max}$) imposed by the lungs (ventilation, Fv, and lung-blood transfer, FL), the cardiovascular system (FQ), and peripheral O_2 diffusion (Fp) were calculated according to a multifactorial model. A reference set of data, describing the status of O_2 transport at maximal exercise in normoxia was used. The effects of $\dot{V}A$ on $\dot{V}_{O_2max}$ were assessed on the assumption of a *constant reference* O_2 flow in mixed venous blood ($\dot{Q}\bar{v}_{O_2}$). The changes in reference data after given independent changes in $\dot{V}A$ were calculated by an iterative procedure, until the $\dot{V}_{O_2max}$ value compatible with the *constant reference* $Q\bar{v}_{O_2}$ was found, at PI_{O_2} values of 150 (normoxia), 130, 110 and 90 Torr. The $\dot{V}_{O_2max}$ changes in normoxia were less than expected assuming a linear O_2 transport system, because of the flatness of the O_2 dissociation curve around normoxic P_{O_2}. This affected the cardiovascular resistance to O_2 flow, and its changes counterbalanced the effects on $\dot{V}_{O_2max}$ of induced changes in $\dot{V}A$. This phenomenon was reversed in hypoxia, as the steep part of the O_2 dissociation curve was approached. The fractional limitations to $\dot{V}_{O_2max}$ in normoxia resulted as follows: Fv and FL provided between 5 and 12%, FQ between 59 and 78%, and Fp between 13 and 19% of the overall $\dot{V}_{O_2max}$ limitation. In hypoxia, Fv and FL increased and FQ decreased. At PI_{O_2} = 90 Torr, when $\dot{V}A$ was halved, Fv, FL, FQ and Fp amounted to 0.35, 0.31, 0.20 and 0.14, respectively.

Key words: Exercise, O_2 transport; Mammals, humans; Model, O_2 transport exercise; Oxygen, transport, exercise

1. Introduction

The maximal O_2 consumption ($\dot{V}_{O_2max}$) is defined by the plateau attained by the O_2 consumption above a given power. Since Hill and Lupton (1923), the limitation to $\dot{V}_{O_2max}$ was usually attributed to the cardiovascular O_2 transport system, at least during exercise involving big muscle groups (Blomqvist and Saltin, 1983; Ekblom, 1986; Margaria et al., 1965).

In recent years, a different approach to the subject of $\dot{V}_{O_2max}$ limitation was proposed. The O_2 conductance equation, a non-linear[1] solution of which was firstly proposed by Shephard (1969), was applied to the description of the O_2 transport system during

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[1] In the present context, 'non-linear' is used to mean that the equation contains a variable coefficient.

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maximal exercise (Taylor and Weibel, 1981). A multifactorial model of $\dot{V}_{O_2max}$ limitation was developed afterwards, on the assumption that each physiological resistance to the O_2 flow from ambient air to the mitochondria provides a given measurable fraction of the overall $\dot{V}_{O_2max}$ limitation (Cerretelli and di Prampero, 1987; di Prampero, 1985; di Prampero and Ferretti, 1990). These authors, by applying present Eq. (2) (see below), calculated that cardiovascular O_2 transport may provide about 70% of the overall $\dot{V}_{O_2max}$ limitation.

A different approach to the analysis of $\dot{V}_{O_2max}$ limitation was proposed by Wagner (1992), who looked at a two-site system (perfusion vs diffusion), and stressed the role of peripheral O_2 diffusion as a factor limiting $\dot{V}_{O_2max}$. An algebraic model of this system was recently developed (Wagner, 1993), by applying the diffusive-convective interaction equations (Piiper and Scheid, 1981; Piiper et al., 1984).

Both the above-cited analyses disregarded the lungs as a possible specific source of $\dot{V}_{O_2max}$ limitation. On one hand, Wagner (1993), although he assumed a linear diffusion-limited lung O_2 transfer, discussed his results in terms of an overall O_2 delivery, that included also an oversimplified cardiovascular O_2 transport with a linear O_2 dissociation curve. On the other hand, di Prampero and Ferretti (1990) postulated that the changes of the resistances to O_2 flow located in the lungs could not influence $\dot{V}_{O_2max}$ in normoxia because inevitably associated with opposite equivalent changes in cardiovascular O_2 transport. This hypothesis, while excluding the lungs from a numerical analysis of the factors limiting $\dot{V}_{O_2max}$, implies the qualitative assumption of a non-linear O_2 transport system.

The role of the lungs in limiting $\dot{V}_{O_2max}$ in normoxic and hypoxic humans is examined in the present study. The readjustments occurring along the O_2 transport system after acute variations of the ventilatory resistance to O_2 flow, and their effects on $\dot{V}_{O_2max}$, are quantified. The fractional limitation of $\dot{V}_{O_2max}$ is then calculated for the first time along the entire O_2 transport system, according to the multifactorial model (di Prampero, 1985; di Prampero and Ferretti, 1990). Thus, this study represents a step beyond previous analyses, that looked only at the linear interrelation between cardiovascular O_2 transport and tissue O_2 utilisation.

2. The general model

A detailed description of O_2 flow along the O_2 transport system against a number of resistances in series can be found in the literature (Taylor and Weibel, 1981; di Prampero, 1985; di Prampero and Ferretti, 1990). Thus only some critical features are reckoned hereafter.

The overall resistance to O_2 flow ($R_T = 1/G_T$, where G indicates conductance) is considered equal to the sum of four physiological resistances in series, associated with alveolar ventilation (ventilatory resistance, $R_V = 1/G_V$), alveolar-capillary O_2 transfer (lung resistance, $R_L = 1/G_L$), blood O_2 transport (circulatory resistance, $R_Q = 1/G_Q$), and peripheral O_2 diffusion and utilisation (peripheral resistance, $R_p = 1/G_p$). At maximal exercise at steady state, the following equalities apply:

$$\dot{V}_{O_2max} = (P_{I_{O_2}} - P_{A_{O_2}})/R_V = (P_{A_{O_2}} - P_{a_{O_2}})/R_L = (P_{a_{O_2}} - P_{\bar{v}_{O_2}})/R_Q = (P_{\bar{v}_{O_2}} - P_{m_{O_2}})/R_p = (P_{I_{O_2}} - P_{m_{O_2}})/R_T \quad (1)$$

where $P_{I_{O_2}}$, $P_{A_{O_2}}$, $P_{a_{O_2}}$, $P_{\bar{v}_{O_2}}$, and $P_{m_{O_2}}$ represent the O_2 partial pressures in inspired air, alveolar air, arterial blood, mixed venous blood, and the mitochondrial matrix, respectively. Each resistance (R_V, R_L, R_Q and R_p) is considered responsible for a fraction of the overall limitation to $\dot{V}_{O_2max}$ (F_V, F_L, F_Q and F_p, respectively, their sum being equal to one). Developing Eq. (1), and expressing in relative terms the changes in $\dot{V}_{O_2max}$ upon changes of the ith resistance to O_2 flow (ΔR_i), di Prampero and Ferretti (1990) ended up with the following linear equation:

$$\frac{\dot{V}_{O_2max}}{(\dot{V}_{O_2max} + \Delta\dot{V}_{O_2max})} = 1 + F_i \cdot \frac{\Delta R_i}{R_i} \quad (2)$$

where F_i is the fractional limitation to $\dot{V}_{O_2max}$ imposed by the resistance in question. Letting $\Delta R_i/R_i = x$, and $\dot{V}_{O_2max}/(\dot{V}_{O_2max} + \dot{V}_{O_2max}) = y$, and generalizing, we obtain:

$$F_i = \frac{dy}{dx} \quad (3)$$

As it stands, Eq. (3) may take any form. Possible

physiological applications of Eq. (3) are described in the next paragraphs.

3. Of a linear respiratory system

Were the O_2 transport along the respiratory system a linear process, Eq. (2) would be applicable and any Fi would be equal to:

$$Fi = \frac{Ri}{RT} = \frac{\Delta Pi}{\Delta PT} \quad (4)$$

whereby the changes in $\dot{V}_{O_2max}$ ensuing from any given acute variation in one Ri could be predicted.

The fractional limitation to $\dot{V}_{O_2max}$ obtained on the basis of Eq. (4) for sedentary men and for endurance athletes in normoxia is shown in Table 1. A linear O_2 transport system implies that FV, FL, FQ and Fp values in Table 1 would remain the same whatever the head O_2 pressure, thus leading to a linear increase in $\dot{V}_{O_2max}$ as a function of PI_{O_2}. This, however, is not the case (Cerretelli, 1980).

The hypothesis of a non-linear behaviour of the O_2 transport system is discussed in the next paragraphs where the effect of induced changes in RV on $\dot{V}_{O_2max}$ are analysed. For this analysis, we used a personal computer (Gateway 2000 486/33C, USA).

Table 1

Fractional limitation to $\dot{V}_{O_2max}$ on the assumption that the O_2 conductance equation has a linear solution

	Sea level sedentary	Sea level endurance athletes
$\dot{V}_{O_2max}$, L min^{-1}	2.90	4.90
PI_{O_2}, Torr	150	150
PA_{O_2}, Torr	120	115[b]
Pa_{O_2}, Torr	95	83[b]
$P\bar{v}_{O_2}$, Torr	20[a]	18[b]
Pm_{O_2}, Torr	0	0
FV	0.20	0.23
FL	0.17	0.21
FQ	0.50	0.43
Fp	0.13	0.12

Experimental data at lea level are average values from Cerretelli and di Prampero (1987), except [a] (Turner et al., 1993) and [b] (Dempsey et al., 1984).

Microsoft Excel 4.0 and Microcal Origin 2.24 softwares were used for data treatment and graphical analysis.

4. Basic data: assumptions and calculations

Let us take a young healthy subject, with $\dot{V}_{O_2max}$ in normoxia (PI_{O_2} = 150 Torr) of 2.9 L min^{-1} (Cerretelli and di Prampero, 1987), and blood haemoglobin concentration (Hb) of 150 g L^{-1}. Reference GV is assumed to be 100 ml min^{-1} Torr^{-1} (RV = 10 Torr min L^{-1} STPD, $\dot{V}_A$ = 92 L min^{-1} BTPS). Then PA_{O_2} is calculated as:

$$PA_{O_2} = PI_{O_2} - \dot{V}_{O_2max} \cdot RV \quad (5)$$

Reference Pa_{O_2} at maximal exercise is assumed to be 95 Torr (Cerretelli and di Prampero, 1987). Assuming a steady-state for gas exchange, RL can be calculated from Eq. (1). The obtained RL value (8.97 Torr min L^{-1}) is kept constant along the entire simulation.

The 'physiological' arterial O_2 saturation (Sa_{O_2}) is calculated from Pa_{O_2} by means of the O_2 status algorithm (Siggaard-Andersen and Siggaard-Andersen, 1990), that takes into account the Bohr effect. To do this, we assumed that: (1) lactic acid at maximal exercise is accumulated at a constant rate, its average concentration being 8 mM; (2) lactic acid dissociation is complete in the range of blood pH; (3) resting blood bicarbonate concentration is 24 mM, and decreases stoichioimetrically with lactic acid accumulation; (4) the gas exchange ratio is 1; and (5) alveolar and arterial CO_2 partial pressures (PA_{CO_2} and Pa_{CO_2}, respectively) are equal. If this is so, Pa_{CO_2} can be calculated as:

$$Pa_{CO_2} = PA_{CO_2} = \dot{V}CO_2 \cdot RV = \dot{V}_{O_2max} \cdot RV \quad (6)$$

Arterial blood pH can then be obtained from the Henderson-Hasselbalch equation. Arterial O_2 concentration (Ca_{O_2}, ml O_2 L^{-1}) is calculated from Hb and Sa_{O_2} as:

$$Ca_{O_2} = 1.34\ Hb\ Sa_{O_2} \quad (7)$$

where 1.34 is the physiological O_2 binding coefficient of haemoglobin. Maximal cardiac output ($\dot{Q}$) is assumed to be constant and equal to 20 L min^{-1}. Mixed venous O_2 concentration ($C\bar{v}_{O_2}$) is then

calculated from the Fick equation. For a respiratory quotient of 1, the CO_2 concentration in mixed venous blood ($C\bar{v}_{CO_2}$) is given by:

$$C\bar{v}_{CO_2} = Ca_{CO_2} + \frac{\dot{V}_{CO_2}}{\dot{Q}} = Ca_{CO_2} + \frac{\dot{V}_{O_2max}}{\dot{Q}} \quad (8)$$

Mixed venous CO_2 partial pressure ($P\bar{v}_{CO_2}$) is then calculated from the CO_2 dissociation curve for reduced blood, and mixed venous blood pH by means of the Henderson-Hasselbalch equation. This allows computation of mixed venous O_2 partial pressure ($P\bar{v}_{O_2}$) from $C\bar{v}_{O_2}$ by means of the O_2 status algorithm. The O_2 transport coefficient of blood is then calculated as:

$$\beta_b = \frac{(Ca_{O_2} - C\bar{v}_{O_2})}{(Pa_{O_2} - P\bar{v}_{O_2})} \quad (9)$$

after which GQ and its reciprocal, RQ, can be calculated. Finally the product of $\dot{Q}$ times $C\bar{v}_{O_2}$ provides the O_2 flow in mixed venous blood ($\dot{Q}\bar{v}_{O_2}$), for which a value of 1.011 min^{-1} is obtained.

The values of all the assumed and calculated variables described in this paragraph for a condition in which PI_{O_2} = 150 Torr, Rv = 10 Torr min L^{-1} and $\dot{V}_{O_2max}$ = 2.9 $L \cdot min^{-1}$, here defined as the reference condition in normoxia, are reported in Table 2.

5. The effects of a change in Rv on $\dot{V}_{O_2max}$

5.1. Normoxia

For any given imposed change in Rv, starting from the reference condition, $\dot{V}_{O_2max}$ and related pa-

Table 2

Reference values for all computed parameters in normoxia for a ventilatory resistance to O_2 flow (Rv) equal to 10 Torr min L^{-1}, and the ensuing values after Rv is increased to 12.5 Torr min L^{-1} or decreased to 7.5 Torr min L^{-1}

Parameter	Symbol	Unit	Value		
			Rv = 10	Rv = 12.5	Rv = 7.5
Inspired O_2 partial pressure	PI_{O_2}	Torr	*150*	150	150
Maximal O_2 uptake	$\dot{V}_{O_2max}$	L min^{-1} (STPD)	*2.90*[a]	2.84	2.95
O_2 transfer coefficient for gas	β_g*	mlO_2 L^{-1} $Torr^{-1}$	*1.16*[a]	1.16	1.16
Alveolar ventilation	$\dot{V}_A$	L min^{-1} (BTPS)	*92.0*	73.9	123.9
Alveolar O_2 partial pressure	PA_{O_2}	Torr	*121*	115	128
Lung resistance to O_2 flow	RL*	Torr min L^{-1}	*8.97*	8.97	8.97
Arterial O_2 partial pressure	Pa_{O_2}	Torr	*95*[a]	89	101
Arterial CO_2 partial pressure	Pa_{CO_2}	Torr	*29.0*	35.5	22.2
Arterial pH	pH_a	unitless	*7.383*	7.295	7.500
Arterial CO_2 concentration	Ca_{CO_2}	$mlCO_2$ L^{-1}	*43.6*	46.2	40.9
Haemoglobin concentration	Hb*	g L^{-1}	*150*[a]	150	150
Arterial O_2 saturation	Sa_{O_2}	unitless	*0.973*	0.958	0.984
Arterial O_2 concentration	Ca_{O_2}	mlO_2 L^{-1}	*195.5*	192.5	197.9
Cardiac output	$\dot{Q}$*	L min^{-1}	*20*[a]	20	20
Mixed venous O_2 partial pressure	$C\bar{v}_{O_2}$	mlO_2 L^{-1}	*50.5*	50.5	50.5
Mixed venous O_2 saturation	$S\bar{v}_{O_2}$	unitless	*0.251*	0.251	0.251
Mixed venous CO_2 concentration	$C\bar{v}_{CO_2}$	$mlCO_2$ L^{-1}	*58.1*	60.4	55.6
Mixed venous CO_2 partial pressure	$P\bar{v}_{CO_2}$	Torr	*51.3*	57.0	45.0
Mixed venous pH	$pH\bar{v}$	unitless	*7.136*	7.090	7.193
Mixed venous O_2 partial pressure	$P\bar{v}_{O_2}$	Torr	*16.9*	17.2	16.5
O_2 transfer coefficient for blood	β_b	mlO_2 M^{-1} $Torr^{-1}$	*1.86*	1.94	1.74
Cardiovascular resistance to O_2 flow	RQ	Torr min L^{-1}	*26.9*	25.3	28.6
O_2 flow in mixed venous blood	$\dot{Q}\bar{v}_{O_2}$*	L min^{-1}	*1.011*	1.011	1.011

Asterisks indicate assumed constants. Exponents indicate either an assumed value or an average from the literature. The reference condition is indicated in italic. The 1.16 figure for β_g is BTPS.

rameters are calculated by trial and error, until the values compatible with the constancy of $\dot{Q}\bar{v}_{O_2}$ are found and retained. The $\dot{V}_{O_2max}$ values ensuing from numerous imposed changes in Rv are shown in Table 3, together with the characteristics of the cardiovascular O_2 transport. Note that the lower is Rv, the higher is RQ, so that RT and $\dot{V}_{O_2max}$ change very little. In Fig. 1, the relative changes in $\dot{V}_{O_2max}$ are plotted as a function of the corresponding changes in Rv. Fig. 1 is equivalent to the Fig. 2 of di Prampero and Ferretti (1990), using Rv instead of RQ. Fv is the first derivative of the general form of Eq. (2) which is complex and unpredictable on physiological grounds. An average Fv value for a given change in Rv can be obtained from the average slope of the curve in Fig. 2 between two points, as:

$$\left[\frac{\dot{V}_{O_2max}}{(\dot{V}_{O_2max} + \Delta\dot{V}_{O_2max})} - 1\right]\frac{Rv}{\Delta Rv} = Fv \quad (10)$$

which is nothing but a discrete solution of Eq. (2) for Fv.

5.2. *Hypoxia*

In hypoxia, the reference $\dot{V}_{O_2max}$ and the $\dot{V}_{O_2max}$ values ensuing from given $\dot{V}A$ changes, are estimated by the same procedure as in normoxia. PI_{O_2} values of 130, 110 and 90 Torr are tested. RL is assumed to remain unchanged. The reference Rv is 10 Torr min L^{-1}, as in normoxia. $\dot{Q}$ and lactate concentration are assumed not to vary in hypoxia. In addition, it is assumed that no further hyperventilation due to direct hypoxic stimulation of the peripheral chemoreceptors occurs, at least down to the tested PI_{O_2} and Pa_{O_2} (Ward and Robbins, 1987). $\dot{Q}\bar{v}_{O_2}$ is assumed to be 1.011 L min^{-1} and constant, as in normoxia (Ferretti et al., 1993). In spite of these constraints, the decrease of the reference $\dot{V}_{O_2max}$ in hypoxia turns out equivalent to that reported in the classical $\dot{V}_{O_2max}$ vs PI_{O_2} plot (Cerretelli, 1980). The results obtained in hypoxia are shown in Fig. 2, where the $\dot{V}_{O_2max}$ ratio is plotted as a function of the induced changes in Rv, for four levels of PI_{O_2}. The changes in Fv as a function of the estimated Pa_{O_2} are shown in Fig. 3.

6. Fractional limitation of maximal O_2 consumption

The fractional limitation of $\dot{V}_{O_2max}$ is estimated after induced changes in Rv only, but these are inevitably associated with opposite changes in RQ. This appears to be a consequence of the curvilinear shape of the O_2 dissociation curve, whose average slope is the term β_b (see Eq. (9)). An increase in ventilation leads to higher PA_{O_2} and hence Pa_{O_2} values, but it does not affect Ca_{O_2} in normoxia, so that

Table 3

Changes in V_{O_2max} and related parameters after given changes in the ventilatory resistance to O_2 flow (Rv)

Rv (Torr min L^{-1})	$\dot{V}_{O_2max}$ (L min^{-1})	PA_{O_2} (Torr)	Pa_{O_2} (Torr)	Ca_{O_2} (mlO_2 L^{-1})	$C\bar{v}_{O_2}$ (mlO_2 L^{-1})	$P\bar{v}_{O_2}$ (Torr)	β_b (mlO_2 L^{-1} $Torr^{-1}$)	RQ (Torr min L^{-1})
20.0	2.59	98.1	74.9	180.3	50.5	18.0	2.28	21.9
17.5	2.68	102.9	78.9	184.7	50.5	17.8	2.20	22.8
15.0	2.77	108.5	83.7	188.9	50.5	17.5	2.09	23.2
12.5	2.84	114.5	89.0	192.3	50.5	17.2	1.98	25.3
10.5	2.89	119.6	93.7	195.0	50.5	17.0	1.88	26.6
10.0	*2.90*	*121.0*	*95.0*	*195.5*	*50.5*	*16.9*	*1.86*	*26.9*
9.1	2.92	123.5	97.3	196.5	50.5	16.8	1.81	27.6
7.5	2.95	127.8	101.4	197.9	50.5	16.5	1.74	28.7
6.7	2.96	130.3	103.7	198.5	50.5	16.4	1.69	29.5
5.0	2.98	135.1	108.4	199.6	50.5	16.2	1.62	30.9
4.0	2.99	138.0	111.2	200.1	50.5	16.1	1.57	31.8

The reference condition (Rv = 10 Torr min L^{-1}) is indicated in italics.

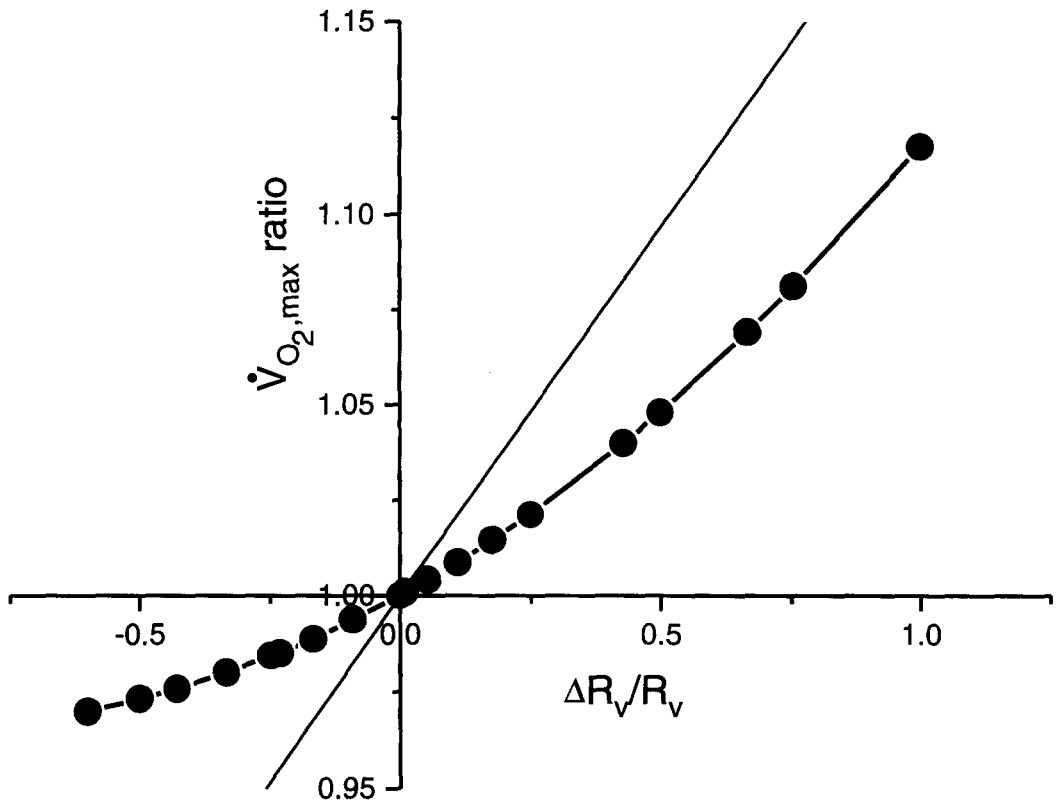

Fig. 1. Changes in maximal O_2 consumption ($\dot{V}_{O_2max}$) induced by acute changes in alveolar ventilation, expressed as the ratio between the $\dot{V}_{O_2max}$ before and the $\dot{V}_{O_2max}$ after the manipulation, are plotted as a function of the changes in the ventilatory resistance to O_2 flow (Rv), expressed as ΔRv/Rv, id est Rv after minus Rv before, the difference divided by Rv before. $\dot{V}_{O_2max}$ ratios above 1 reflect a decrease in $\dot{V}_{O_2max}$ and ΔRv/Rv above zero reflect an increase in Rv. The results of the present analysis in normoxia are connected by the thick curve. The thin line represents the relationship that would apply in the case of a linear O_2 transport system.

β_b decreases. It is the ensuing change in RQ, shown in Fig. 4 as a function of Rv, that prevents $\dot{V}_{O_2max}$ from varying linearly with the Rv variations. This reasoning may explain the shape of the curve shown in Fig. 1. In fact, were the O_2 dissociation curve linear, the changes in $\dot{V}_{O_2max}$ following any change in Rv would be represented by the thin line in the same figure, and Fv would be a constant that could be calculated from Eq. (4). The difference between the thin and thick lines in Fig. 1 reflects the apparent effect of the shape of the O_2 dissociation curve on the fractional limitation to $\dot{V}_{O_2max}$ imposed by pulmonary ventilation.

However, as PI_{O_2} decreases, Pa_{O_2} progressively shifts towards the steeper part of the O_2 dissociation curve, so that 1) β_b becomes higher than in normoxia, with subsequent lower RQ, and 2) no further compensation of Rv changes by RQ is possible. The former corollary is reflected in the classical non-linear $\dot{V}_{O_2max}$ vs PI_{O_2} plot (Cerretelli, 1980): any decrease in PI_{O_2} is necessarily accompanied, because of the shape of the O_2 dissociation curve, by a reduction in RQ, and thus in RT, that leads to higher $\dot{V}_{O_2max}$ values than predicted on the basis of an invariant RT. In addition, the latter corollary implies that the O_2 transport system in hypoxia approaches linearity around Fv (FQ) values that are greater (lower) than those computed in normoxia. This is shown in Fig. 2, where a drop in PI_{O_2} is accompanied by a reduced concavity of the plotted curves, whose slopes, that are equal to Fv, increase, becoming progressively higher than that of the hypotheti-

cal line calculated assuming a linear O_2 transport system with a reference normoxic β_b.

Since the sum of all FIs is always equal to one, the changes in FV shown by the curves in Figs. 1 and 2 imply rearrangement of all other FIs. Define then an overall pulmonary resistance, RPU = RV + RL, from which an overall pulmonary fractional limitation to $\dot{V}_{O_2max}$, FPU (= FV + FL) can be predicted. Changes in FPU following changes in RV can be estimated from Eq. (10) after substituting RPU instead of RV and FPU instead of FV. FL can then be calculated as FPU − FV. FQ and FP are then calculated on the assumption that the O_2 transfer across RQ and RP, at any P_{O_2} level, is linear, in which case:

$$FQ = \frac{(Pa_{O_2} - P\bar{v}_{O_2})}{Pa_{O_2}} (1 - FPU) \quad (11)$$

FP is then obtained by subtraction of all other FI values from one. The overall average fractional limitation to $\dot{V}_{O_2max}$ in normoxia resulting from the above described calculations is given in Table 4. Fig. 5 summarizes the readjustments of FQ, FP and FV as a function of PI_{O_2}, calculated for 4 changes in RV from the reference condition. It appears that in normoxia most of the $\dot{V}_{O_2max}$ limitation is provided by FQ, but at PI_{O_2} = 90 Torr the fractional limitation to $\dot{V}_{O_2max}$ is almost equally partitioned among the four considered FI values.

It is noteworthy that the present results, whose validity relies on the multifactorial model of $\dot{V}_{O_2max}$ limitation, confirm and reinforce the conclusions arrived at by Piiper and Scheid (1981) who first stressed the role of diffusion resistance in lungs as limiting $\dot{V}_{O_2max}$ in hypoxia on the basis of the two-site perfusive-convective gas exchange model.

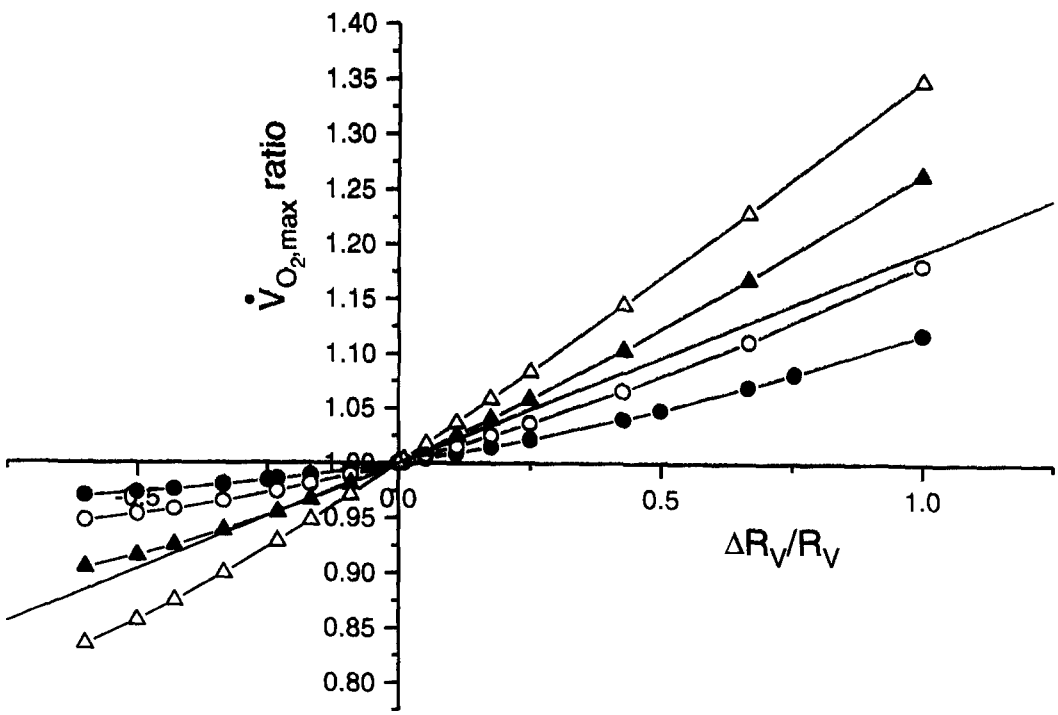

Fig. 2. Same as in Fig. 1, but at various P_{O_2} values (inspired P_{O_2}, PI_{O_2} of 150, 130, 110 and 90 Torr for ●, ○, ▲ and △, respectively). The straight line represents the relationship applying in the case of a linear O_2 transport system for an O_2 transfer coefficient for blood equivalent to that of the reference condition in normoxia. $\dot{V}_{O_2max}$ ratios above 1 reflect a decrease in $\dot{V}_{O_2max}$ and ΔRV/RV above zero reflect an increase in RV.

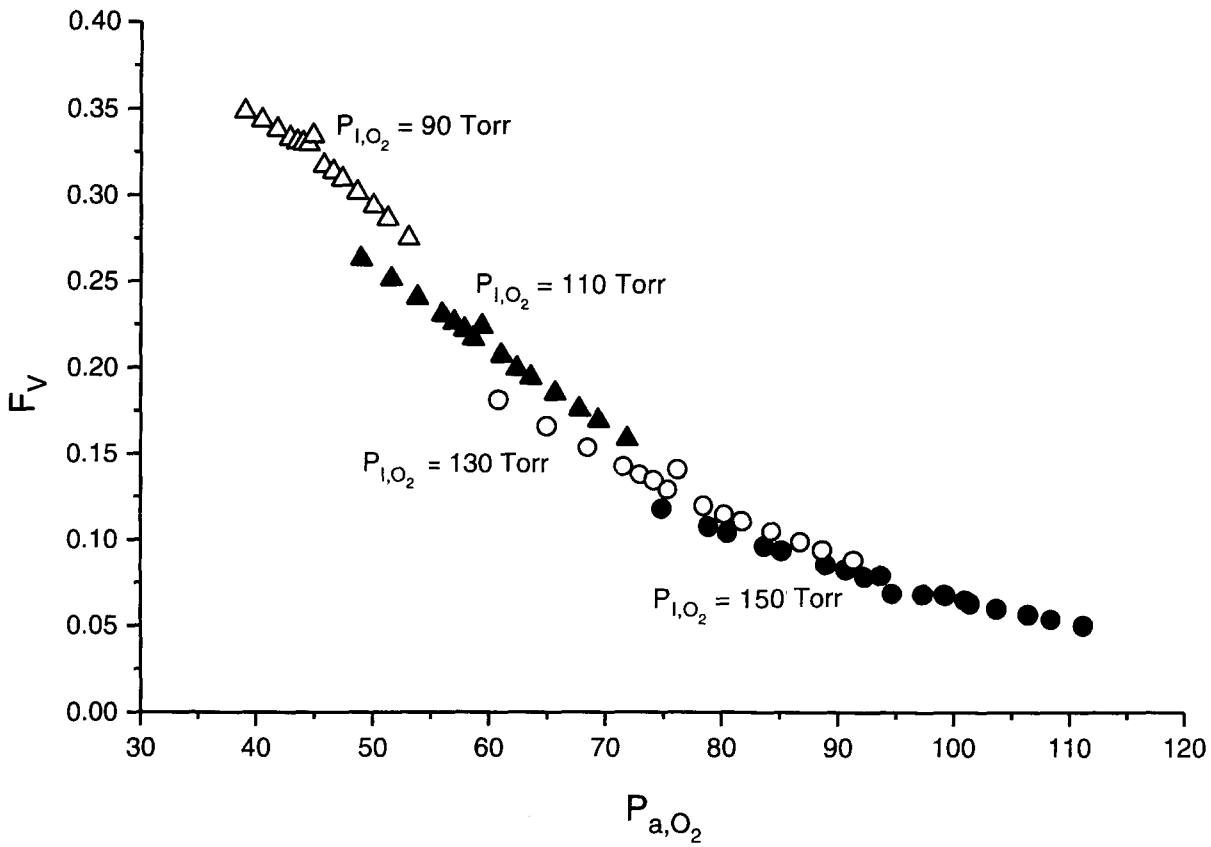

Fig. 3. Fractional limitation to maximal O_2 consumption imposed by alveolar ventilation (Fv) as a function of arterial P_{O_2} (Pa_{O_2}), at the indicated inspired P_{O_2} (PI_{O_2}). Each point corresponds to a given change in the ventilatory resistance to O_2 flow.

7. Model's limitation: critique of assumptions

The multifactorial model of $\dot{V}_{O_2max}$ limitation analysed in this study is characterized by its simplicity, which, however, may per se restrict its applicability. In addition, the simulation, although extending the results obtained in previous studies (di Prampero, 1985; di Prampero and Ferretti, 1990), yet represents a particular case, in view of the constraints imposed by the assumptions made. A critique of assumptions is attempted in the following paragraphs.

7.1. Constancy of $\dot{Q}\bar{v}_{O_2}$ and of cardiac output

Most critical is the assumption of a constant $\dot{Q}\bar{v}_{O_2}$ in any condition. This assumption relies on the

Table 4

Fractional limitation of $\dot{V}_{O_2max}$ in normoxia, calculated from a reference Rv of 10 Torr min LO_2^{-1}

ΔRv (Torr min LO_2^{-1})	Fv	FL	FQ	Fp	$\Delta\dot{V}_{O_2max}$ (L min^{-1})
10.0	0.118	0.106	0.589	0.187	−0.306
7.5	0.108	0.097	0.616	0.179	−0.218
5.0	0.096	0.086	0.647	0.171	−0.133
2.5	0.085	0.077	0.676	0.162	−0.060
0.5	0.079	0.071	0.696	0.154	−0.012
−0.9	0.068	0.061	0.721	0.150	0.018
−2.5	0.065	0.058	0.733	0.144	0.046
−3.3	0.060	0.054	0.746	0.140	0.059
−5.0	0.054	0.048	0.764	0.134	0.080
−6.0	0.050	0.045	0.775	0.130	0.090

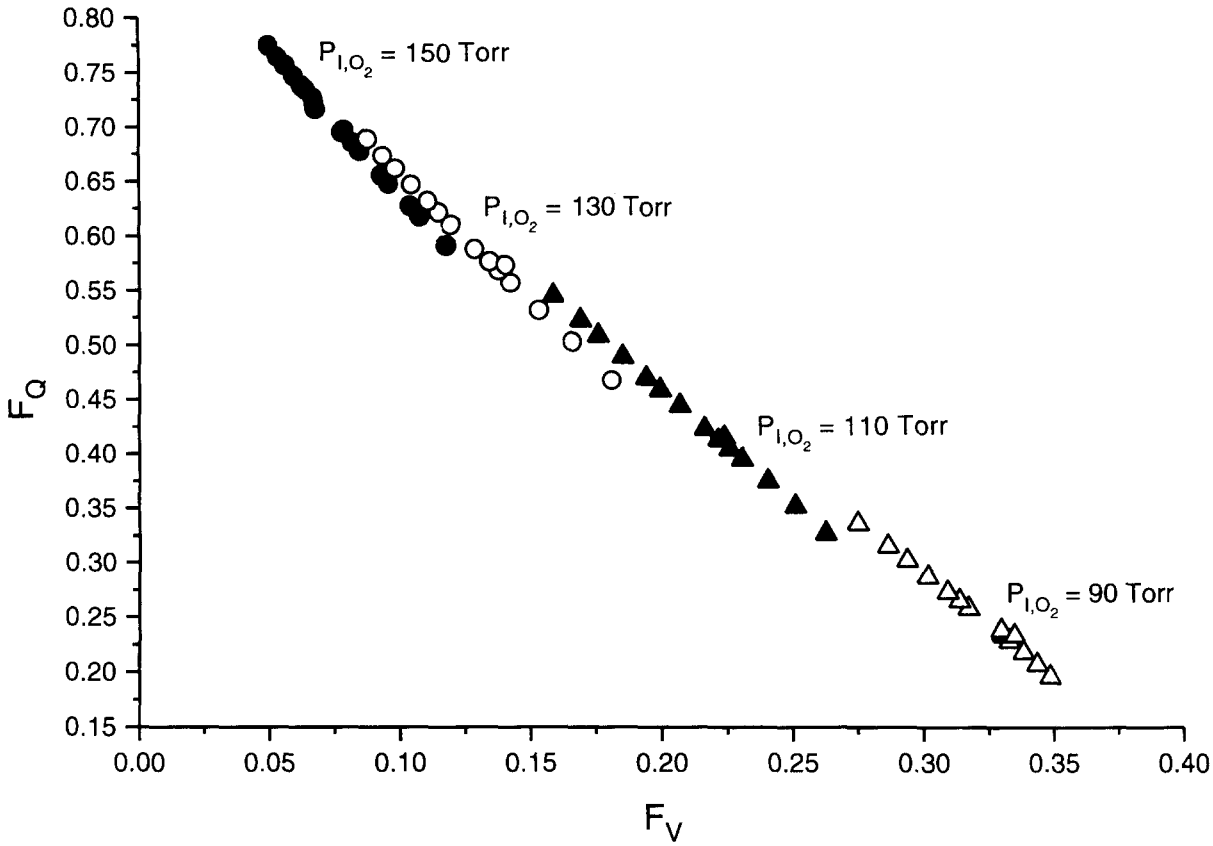

Fig. 4. Fractional limitation to $\dot{V}_{O_2max}$ imposed by the circulatory resistance to O_2 flow (FQ) as a function of fractional limitation to $\dot{V}_{O_2max}$ imposed by the ventilatory resistance to O_2 flow (FV), at the indicated inspired P_{O_2} (PI_{O_2}).

observation that arterial O_2 flow ($\dot{Q}a_{O_2}$) during exercise was related to the mechanical power output by a straight line with a slope equal to that of the VO_2 vs power ($\dot{w}$) line (Ferretti et al., 1992). This implies that the difference between $\dot{Q}a_{O_2}$ ($\dot{w}$) and $\dot{V}_{O_2}$ ($\dot{w}$), i.e. $\dot{Q}\bar{v}_{O_2}$, is a constant. Yet hypoxia may interfere with the alleged control system of the cardiovascular response to exercise by hypoxaemic stimulation of peripheral chemoreceptors, that besides inducing hyperventilation, is known to affect the heart function. This could lead to expect Pa_{O_2}-related changes in $\dot{Q}\bar{v}_{O_2}$. However, this is not the case, at least down to PI_{O_2} levels around 80 Torr (Ferretti et al., 1993).

Obviously enough, the hypothesis of a constant $\dot{Q}\bar{v}_{O_2}$ must apply also when maximal $\dot{Q}$ is let to vary freely. In the present study, however, also $\dot{Q}$ has been forcefully maintained constant, in order to stress the role of β_b in the RQ changes induced by varying RV. As a consequence, $C\bar{v}_{O_2}$ turns out the same in all examined conditions. Yet, the constraint of a constant $\dot{Q}$ at maximal exercise covers a great number of physiological conditions in which specific changes in either RQ or RV are induced (Dempsey et al., 1984; Ekblom et al., 1976; Turner et al., 1993). Also, maximal $\dot{Q}$ in acute hypoxia is the same as in normoxia (Stenberg et al., 1966; Hartley et al., 1973).

7.2. *Mitochondrial P_{O_2}*

In this study, as in others (di Prampero and Ferretti, 1990; Wagner, 1993), Pm_{O_2} is assumed to be zero. Of course, no direct support to this assumption can be obtained. Yet P_{O_2} values of less than 3 Torr in the cytosol of contracting dog muscle fibres

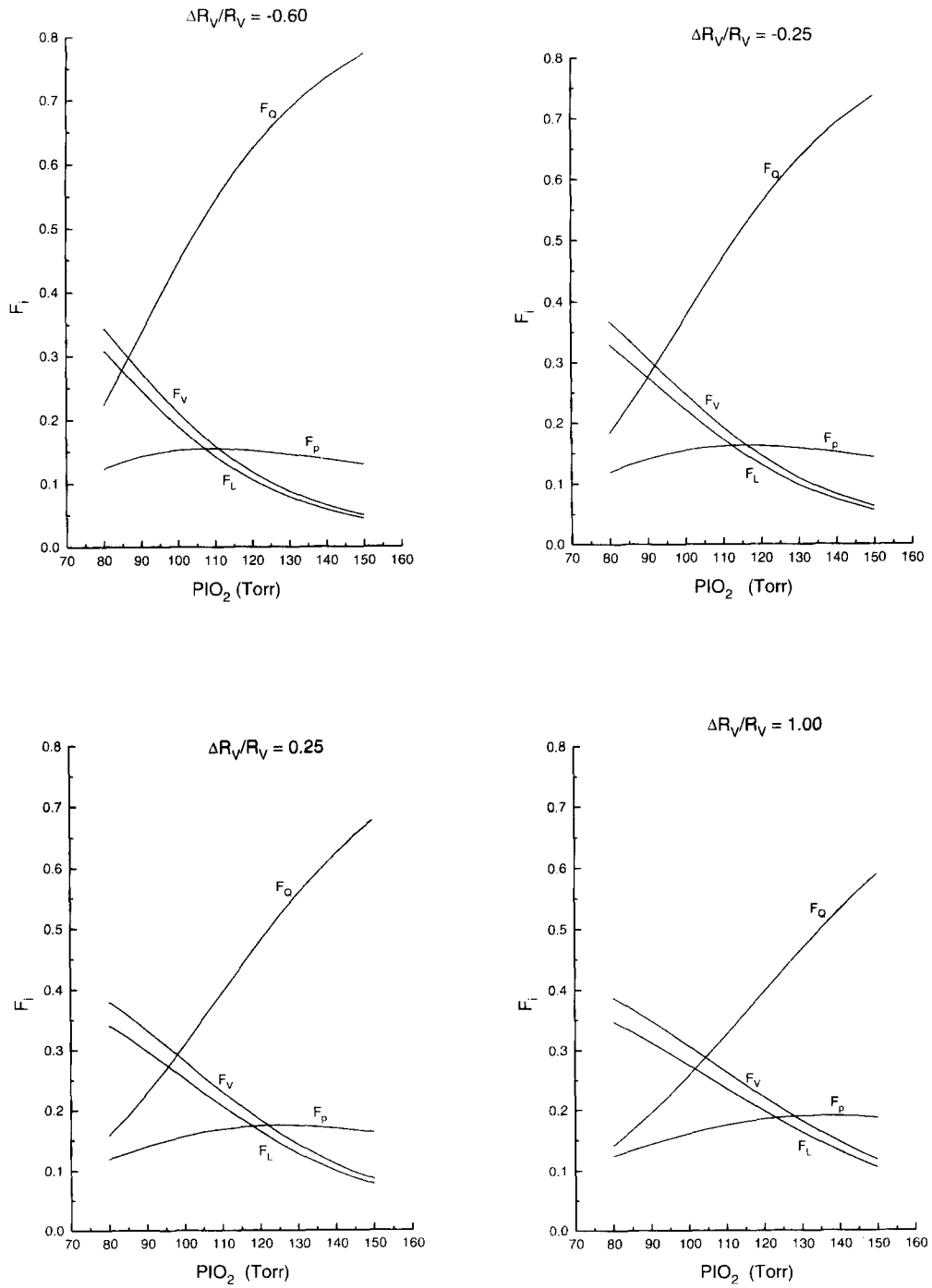

Fig. 5. Fractional limitation to maximal O_2 consumption imposed by the ith resistance to O_2 flow (Fi) as a function of inspired P_{O_2} (PI_{O_2}). Each panel applies for the induced change in ventilatory resistance (Rv) indicated on top. Curves referring to the fractional limitation to $\dot{V}_{O_2max}$ imposed by cardiovascular O_2 transport (FQ), peripheral O_2 transfer (Fp), pulmonary O_2 transfer (FL) and alveolar ventilation (Fv) are shown.

have been reported (Gayeski and Honig, 1988), which indirectly argues in favour of the present assumption. In any case, a Pm_{O_2} of 3 Torr, which seems to be an overestimate, would affect RT by no more than 3.4% (at $PI_{O_2} = 90$ Torr), with negligible effects on the fractional limitation of $\dot{V}_{O_2max}$.

7.3. Constancy of lung resistance to O_2 flow

The assumption of a constant RL value has the clear advantage of allowing a neat identification of the strict connections existing between RV and RQ and of their effects on $\dot{V}_{O_2max}$ limitation. Yet this assumption represents an oversimplification. In fact it can be shown that (see e.g. Piiper and Scheid, 1981)

$$\frac{PA_{O_2} - Pa_{O_2}}{PA_{O_2} - P\bar{v}_{O_2}} = \frac{RL}{RL + RQ} = \exp\left(-\frac{DL_{O_2}}{\dot{Q}\cdot\beta_b}\right) \quad (12)$$

where DL_{O_2} is the lung diffusing capacity for O_2, whereby RL appears to be affected by β_b. In the reference condition, the error introduced on RL by assuming RL constant, with present β_b values, would be +11.1%, +23.8% and +37.1% at PI_{O_2} of 130, 110 and 90 Torr, respectively. On the other hand taking a constant RL when varying RV in normoxia implies an error comprised between +9.5% and −7.7% (two extremes of RV). This error, however, disappears in hypoxia, as the oxygen dissociation curve approaches linearity.

These errors on RL would affect either Pa_{O_2}, so that a different equilibrium is attained, with an RQ error compensating for the RL error, or RT, or both. The latter case would imply an underestimate of $\dot{V}_{O_2max}$ in the reference condition (−1.9%, −4.3% and −6.8% at PI_{O_2} of 130, 110 and 90 Torr, respectively), with slight but unessential effects on the Fis and on the shape of the curves in Fig 5.

8. Physiological consequences and predictions

The results of Table 4 and Fig. 1 support the hypothesis that the lungs provide negligible V_{O_2max} limitation in normoxia. In fact, it appears that at least a 60% reduction in R_v is required to obtain a 10% increase in $\dot{V}_{O_2max}$, and that a 10% decrease in RV results in a $\dot{V}_{O_2max}$ change within the experimental error. This leads to the prediction that, if one reduces RV by means of almitrin bismesylate (Giesbrecht et al., 1991), or by breathing He-O_2 mixtures (Dempsey et al., 1984), very little $\dot{V}_{O_2max}$ increases should be found in normoxia.

This prediction may be contradicted by endurance athletes, who have extremely high $\dot{V}_{O_2max}$ and $\dot{Q}$ values. In fact, they were shown to undergo a significant arterial blood desaturation at maximal exercise in normoxia (Dempsey et al., 1984; Williams et al., 1986) with Pa_{O_2} and Sa_{O_2} values around the steeper part of the O_2 dissociation curve. As a consequence, in endurance athletes, $\dot{V}_{O_2max}$ in normoxia may increase significantly after a reduction in RV. If this is so, (1) the fraction of $\dot{V}_{O_2max}$ limitation provided by the lungs in endurance athletes would be greater than in sedentary subjects, and (2) the slope of the $\dot{V}_{O_2max}$ vs PI_{O_2} relationship should be systematically greater in endurance athletes than in sedentary subjects, because of the respective different changes in Sa_{O_2}. Although the latter hypothesis has not been systematically tested so far, it is not contradicted by the spotty data obtained by Terrados et al. (1985) at altitudes up to 1500 m, and by Lawler et al. (1988) in acute hypoxia (PI_{O_2} of 106 Torr only).

In hypoxia, as shown in Fig. 4, the role played by the lungs in limiting $\dot{V}_{O_2max}$ increases and RQ is lower than in normoxia because of the increase in β_b. As a consequence, a new equilibrium along the respiratory system is attained, whereby the factors limiting $\dot{V}_{O_2max}$ may vary as indicated in Fig. 5. Fig. 5 has numerous physiological consequences. Firstly, in hypoxia, a reduction in RV should have greater effects on $\dot{V}_{O_2max}$, the lower is PI_{O_2} and thus Pa_{O_2}. Second, the effects on $\dot{V}_{O_2max}$ of any manoeuvre acutely altering cardiovascular O_2 transport, such as blood withdrawal or re infusion, should be less the lower is PI_{O_2}. Furthermore, changes in active muscle mass and thus in total muscle blood flow, that affect RP and RQ respectively, as occurs e.g. during exercise with small vs big muscle groups, should have smaller effects on $\dot{V}_{O_2max}$ in hypoxia than in normoxia. In other words, the differences in $\dot{V}_{O_2max}$ between one- vs two-leg exercise should be slightly reduced in hypoxia, whereby the $\dot{V}_{O_2max}$ vs PI_{O_2} relationship may be slightly different in the two exercise modes.

None of the above listed hypotheses have undergone specific experimental verification so far, although some data in the literature, obtained for other purposes, appear compatible with them. After one week at 4300 m above sea level, one-leg $\dot{V}_{O_2max}$ was found to be 91% of two-leg $\dot{V}_{O_2max}$, instead of 81% in normoxia (Fulco et al., 1988). The same authors, however, failed in observing a different $\dot{V}_{O_2max}$ ratio between the two exercise modes in acute hypoxia. In another context, Dempsey et al. (1984) were able to find greater changes in $\dot{V}_{O_2max}$ after He-O_2 breathing in hypoxia than in normoxia. These data, however, are too sparse to provide sufficient experimental background in support of the theoretical analysis carried out in the present study. To get this, one should (1) independently vary one of the physiological resistances to O_2 flow represented in Eq. (1); (2) look at the changes in resistance; (3) look at the resulting changes in $\dot{V}_{O_2max}$; (4) check whether subsequent, dependent changes in RQ may be responsible for some of the changes in $\dot{V}_{O_2max}$, (5) repeat the experiments in normoxia and hypoxia; (6) verify whether the changes in $\dot{V}_{O_2max}$ are compatible with the predictions resulting from the present study. No experiment so far was conceived and realised, that could fulfil all the conditions listed here above.

9. Conclusions

The present analysis shows that pulmonary ventilation and lung O_2 transfer share a small fraction of $\dot{V}_{O_2max}$ limitation in normoxia, most of the limits being imposed by cardiovascular O_2 transport ($\sim 70\%$). As PI_{O_2} decreases, the role of the lungs in limiting $\dot{V}_{O_2max}$ becomes greater and that of the cardiovascular system smaller, the lower is PI_{O_2}. At $PI_{O_2} = 90$ Torr, the lungs (pulmonary ventilation plus lung O_2 transfer) account for the majority of the fractional limitation to $\dot{V}_{O_2max}$, particularly in the range of low ventilation values. These results are a direct consequence of the non-linear blood O_2 loading and unloading due to the sigmoidal shape of the O_2 dissociation curve.

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