The decrease of maximal oxygen consumption during hypoxia in man: a mirror image of the oxygen equilibrium curve

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1. Endurance athletes (E) undergo a marked reduction of arterial O_2 saturation (S_{a,O_2}) at maximal exercise in normoxia, which disappears when they breathe hyperoxic mixtures. In addition, at a given level of hypoxia, the drop in maximal O_2 consumption ($\dot{V}_{O_2,max}$) is positively related to the individual normoxic $\dot{V}_{O_2,max}$.

2. These data suggest that the curve relating $\dot{V}_{O_2,max}$ to P_{I,O_2} may be steeper and perhaps less curved in E than in sedentary subjects (S) with low $\dot{V}_{O_2,max}$ values because of the greater hypoxaemia in the latter, whence the hypotheses that (i) the relationship between $\dot{V}_{O_2,max}$ and P_{I,O_2} may be set by the shape of the oxygen equilibrium curve; and (ii) the differences between E and S may be due to the different position on the oxygen equilibrium curve on which these subjects operate. These hypotheses have been tested by performing a systematic comparison of the $\dot{V}_{O_2,max}$ or S_{a,O_2} vs. P_{I,O_2} relationships in E and S.

3. On ten subjects (five S and five E), $\dot{V}_{O_2,max}$ was measured by standard procedure during cyclo-ergometric exercise. S_{a,O_2} was measured by finger-tip infrared oximetry. Arterialized blood P_{O_2} (P_{a,O_2}) and P_{CO_2} (P_{a,CO_2}) were determined in 80 μl blood samples from an ear lobe. The subjects breathed ambient air or a N_2–O_2 mixture with an inspired O_2 fraction (F_{I,O_2}) of 0·30, 0·18, 016, 013 and 0·11, respectively. $\dot{V}_{O_2,max}$ was normalized with respect to that obtained at the highest F_{I,O_2}.

4. The relationships between S_{a,O_2} or normalized $\dot{V}_{O_2,max}$ and F_{I,O_2} (or P_{I,O_2}) had similar shapes, the data for E being systematically below and significantly different from those for S. Linear relationships between S_{a,O_2} and normalized $\dot{V}_{O_2,max}$, statistically equal between E and S, were found.

5. We conclude that the relationships between either $\dot{V}_{O_2,max}$ or S_{a,O_2} and F_{I,O_2} (or P_{a,O_2}) may indeed be the mirror images of one another, implying a strict link between the decrease of $\dot{V}_{O_2,max}$ in hypoxia and the shape of the oxygen equilibrium curve, as hypothesized.

The classical non-linear relationship between maximal oxygen consumption ($\dot{V}_{O_2,max}$) and inspired oxygen partial pressure (P_{I,O_2}) in hypoxia (Cerretelli, 1980; Ward, Milledge & West, 1989; Ferretti, 1990; Cerretelli & Hoppeler, 1996) was established from data obtained on sedentary or non-athletic individuals, who are characterized by relatively low $\dot{V}_{O_2,max}$ values in normoxia. In spite of this, its shape was considered independent of the maximal working capacity or of the maximal normoxic aerobic power of the tested subjects. However, during maximal exercise in normoxia, most individuals with high $\dot{V}_{O_2,max}$ levels, such as endurance athletes, show an enlarged alveolar to arterial O_2 pressure difference, with a subsequent marked reduction of arterial oxygen pressure (P_{a,O_2}) and saturation (S_{a,O_2}) (Dempsey, Hanson & Henderson, 1984; Williams, Powers & Stuart, 1986; Lawler, Powers & Thompson, 1988; Powers, Lawler, Dempsey, Dodd & Landry, 1989). This condition of hypoxaemia, which might be due either to the very high

pulmonary blood flow of these athletes, leading to an insufficient pulmonary capillary transit time for O_2 equilibration at the alveolar capillary level (Dempsey *et al.* 1984), or to a mechanical limitation of pulmonary ventilation (Johnson, Saupe & Dempsey, 1992), disappears only when these subjects are given hyperoxic mixtures to breathe (Dempsey *et al.* 1984; Powers *et al.* 1989). Furthermore, at a given level of hypoxia, the extent of the decrease in $\dot{V}_{O_2,max}$ was positively related to the individual normoxic $\dot{V}_{O_2,max}$ values (Terrados, Mizuno & Andersen, 1985; Young, Cymerman & Burse, 1985; Williams *et al.* 1986; Lawler *et al.* 1988).

These data suggest that the relationship between $\dot{V}_{O_2,max}$ and P_{I,O_2} may differ between subjects with low and high $\dot{V}_{O_2,max}$ values. In fact the hypoxaemia reported to occur in the latter group of subjects at maximal exercise in normoxia indicates that any decrease in P_{I,O_2}, and thus in P_{a,O_2}, would be accompanied by a greater reduction in arterial oxygen

concentration (C_{a,O_2}), and thus in $\dot{V}_{O_2,max}$, in these individuals than in their sedentary counterparts; and this simply because their normoxic P_{a,O_2} values are already displaced towards the steep part of the oxygen equilibrium curve. This reasoning leads to the formulation of the following hypotheses: (i) the relationship between $\dot{V}_{O_2,max}$ and P_{I,O_2} may be set by the shape of the oxygen equilibrium curve; (ii) this relationship may be steeper and perhaps less curved in endurance athletes than in sedentary subjects; and (iii) these differences may be due to the different position on the oxygen equilibrium curve on which these subjects operate.

In the present experiments, we tested these hypotheses by performing a systematic comparison of the $\dot{V}_{O_2,max}$ vs. P_{I,O_2} and of the S_{a,O_2} vs. P_{I,O_2} relationships in individuals with high and low $\dot{V}_{O_2,max}$ in normoxia. Such a comparison, to our knowledge, has not been performed so far.

A preliminary report of this study has previously been published (Thomet, Kayser, Moia & Ferretti, 1994).

METHODS

Subjects

The experiments, which were approved by the Ethical Committee of the Department of Medicine, University of Geneva, were carried out on a group of ten healthy young males, which consisted of five sedentary subjects (S; age, 33 ± 9 years; height, 1.77 ± 0.06 m; body mass, 73.6 ± 6.1 kg) and five endurance-trained individuals (E; age, 25 ± 7 years; height, 1.76 ± 0.04 m; body mass, 66.3 ± 4.4 kg). Before being admitted to the tests, each subject was informed about the procedures to be followed and the potential risks inherent with the experiments, and signed an informed consent form.

Measurements

The oxygen uptake ($\dot{V}_{O_2}$) was measured at rest and at the metabolic steady state of exercises of increasing intensities on the bicycle ergometer. The lowest powers were 50 and 100 W for S and E, respectively. Power was progressively increased, initially by steps of 50 W, then, as the expected individual maximum power was approached, by steps of 25 W. The duration of exercise at each work load was 5 min. Successive work loads were separated by 5 min intervals, during which blood samples (20 μl) were obtained from an ear lobe at minutes 1, 3 and 5, for determination of blood lactate concentration ([La]$_b$), by means of an electro-enzymatic method (ESAT 6661 Lactat, Eppendorf, Germany).

Expired gas was collected into Douglas bags during the last minute of each work load, and subsequently analysed for gas composition and volume. A paramagnetic oxygen analyser (Oxynos 1-C, Leybold Haereus, Germany), an infrared CO_2 analyser (LB-2, Leybold Haereus) and a dry-gas meter (Singer DTM 15, USA) were used. The $\dot{V}_{O_2}$ was computed by standard procedure. CO_2 output, expired ventilation and the gas exchange ratio (R) were also calculated. Heart rate (f_H), measured by electrocardiography (Elmed, ETM, Germany), was monitored continuously during the entire protocol.

The achievement of individual $\dot{V}_{O_2,max}$ was indicated by the appearance of a plateau in the relationship between $\dot{V}_{O_2}$ and mechanical power. In case such a plateau could not be identified, the following subsidiary criteria indicated $\dot{V}_{O_2,max}$ attainment: (1) a lack of increase in f_H between the two heaviest work loads

($\Delta f_H < 5$ min^{-1}); (2) R values higher than 1.1; (3) [La]$_b$ values higher that 10 mM.

At rest and immediately after the end of the highest work load, an 80 μl arterialized blood sample was obtained from an ear lobe, after having induced local hyperaemia by the application of an ointment (Trafuril, Ciba Geigy, Switzerland), and immediately analysed (Ciba Corning 280 blood gas system, USA) for pH, haemoglobin concentration ([Hb]), P_{a,O_2} and P_{a,CO_2}. S_{a,O_2} was continuously measured by finger-tip infrared oximetry (Pulsox-5, Minolta, Japan).

Protocol

The experiments were performed at a mean barometric pressure of 730 Torr. Ambient temperature was thermostated at 20 °C. Each subject underwent six exercise tests for $\dot{V}_{O_2,max}$ determination. The first test was always carried out in normoxia (ambient air, $P_{I,O_2} = 150$ Torr). In the other tests, the subject breathed inspired oxygen fractions (F_{I,O_2}) of 0.11, 0.13, 0.16, 0.18 and 0.30, (P_{I,O_2}, of 80, 95, 116, 131 and 220 Torr, respectively), administered in random order. Successive experimental sessions on a subject were separated by at least 2 days, in order to prevent specific training effects. When hypoxic or hyperoxic gas mixtures were used, inspired gas was provided by high precision gas cylinders and administered via a Douglas bag, which was used as volume buffer, and a hose, through the inspiratory side of the valve. For each $\dot{V}_{O_2,max}$ determination, F_{I,O_2} was measured next to the inlet valve. Ten minutes at rest were allowed for equilibration with the gas mixture, before carrying out the test.

Data treatment and statistical analysis

The $\dot{V}_{O_2,max}$ values were normalized relative to the value obtained at an F_{I,O_2} of 0.3, set equal to 1. Values are given as means $\pm$ standard error of the mean (s.e.m.). The normalized $\dot{V}_{O_2,max}$ values were compared with the corresponding S_{a,O_2} values by a two-tailed Student's t test for paired observations, the difference being considered significant if $P < 0.05$.

Comparison of data between groups were made either by analysis of variance or by analysis of covariance. A *post hoc* Bonferroni test was used to determine differences between pairs. When applicable, differences between regression lines were assessed by analysis of variance, as described by Kleinbaum, Kupper & Muller (1988). Differences between groups were considered significant if $P < 0.05$.

RESULTS

The relationship between $\dot{V}_{O_2}$ and power at sub maximal exercise was linear, invariant among individuals, and independent of F_{I,O_2} and of the athletic status of the subjects. A linear regression on all $\dot{V}_{O_2}$ data at submaximal exercise yielded a $\dot{V}_{O_2}$ value of 0.37 ± 0.011 W ($n = 251$, $r = 0.988$, $P < 0.001$), from which a mean mechanical efficiency of exercise of 0.261 was obtained.

Measured and calculated metabolic variables at maximal exercise while breathing various F_{I,O_2} values, are presented in Table 1. The parameters describing blood O_2 transport and the blood pH data are shown in Table 2.

At any F_{I,O_2}, both absolute (l min^{-1}) and specific (ml min^{-1} kg^{-1}) $\dot{V}_{O_2,max}$ was higher in E than in S. $\dot{V}_{O_2,max}$ increased as a function of F_{I,O_2} in both groups. Such an increase was curvilinear, with a steeper slope in E than in S,

Table 1. Metabolic variables at maximal exercise

F_{I,O_2}	$\dot{V}_{O_2,max}$ (l min⁻¹)		$\dot{V}_{O_2,max}$ (ml min⁻¹ kg⁻¹)		Normalized $\dot{V}_{O_2,max}$		Power (W)		f_H (beats min⁻¹)		$[La]_b$ (mM)	
	S	E	S	E	S	E	S	E	S	E	S	E
0·30	3·19 ± 0·43	4·43 ± 0·15	43·7 ± 4·0	66·3 ± 3·2	1·000 ± 0·000	1·000 ± 0·000	248 ± 28	361 ± 17	190 ± 6	193 ± 3	13·5 ± 1·3	14·5 ± 1·0
0·21	3·13 ± 0·30	4·11 ± 0·16	42·1 ± 2·6	62·1 ± 1·8	0·998 ± 0·036	0·929 ± 0·030	233 ± 25	342 ± 24	190 ± 5	192 ± 4	12·2 ± 0·3	14·2 ± 0·4
0·18	2·87 ± 0·26	3·82 ± 0·09	39·1 ± 2·3	56·7 ± 2·4	0·919 ± 0·048	0·855 ± 0·023	222 ± 26	321 ± 13	186 ± 7	187 ± 2	13·1 ± 1·0	14·0 ± 0·5
0·16	2·70 ± 0·25	3·56 ± 0·10	36·4 ± 2·4	53·4 ± 1·7	0·869 ± 0·063	0·805 ± 0·016	210 ± 23	286 ± 12	183 ± 9	188 ± 4	12·3 ± 0·9	13·2 ± 0·4
0·13	2·27 ± 0·29	2·92 ± 0·07	30·7 ± 3·1	43·9 ± 0·8	0·727 ± 0·069	0·661 ± 0·021	169 ± 25	250 ± 10	179 ± 8	186 ± 4	11·2 ± 1·4	14·7 ± 0·5
0·11	1·96 ± 0·17	2·38 ± 0·04	26·5 ± 1·7	35·6 ± 1·3	0·635 ± 0·053	0·540 ± 0·022	150 ± 14	199 ± 6	167 ± 10	180 ± 3	11·5 ± 1·3	13·1 ± 0·7

S, sedentary subjects; E, endurance-trained subjects; F_{I,O_2}, inspired O_2 fraction; $\dot{V}_{O_2,max}$, maximal O_2 consumption; f_H, heart rate; $[La]_b$, blood lactate concentration. Data are given as means ± S.E.M.
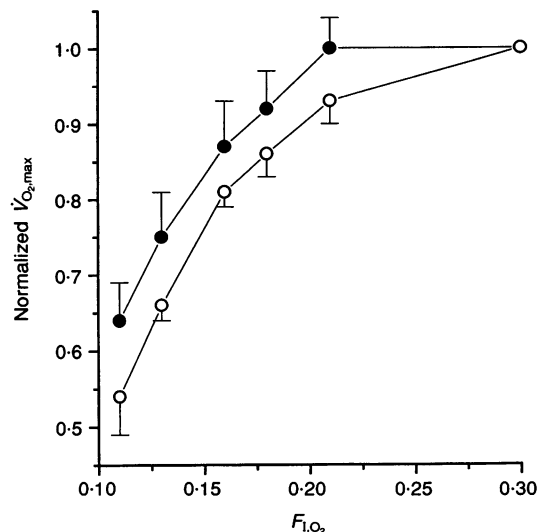
Table 2. Blood oxygen transport parameters and blood pH data at maximal exercise

F_{I,O_2}	P_{a,O_2} (mmHg)		[Hb] (g l⁻¹)		S_{a,O_2}		pH (pH units)	
	S	A	S	A	S	A	S	A
0·30	128·3 ± 8·5	109·6 ± 6·9	162 ± 3	162 ± 2	0·982 ± 0·001	0·968 ± 0·003	7·24 ± 0·03	7·16 ± 0·02
0·21	93·0 ± 2·6	82·5 ± 3·4	163 ± 2	158 ± 3	0·958 ± 0·0051	0·930 ± 0·010	7·26 ± 0·01	7·15 ± 0·02
0·18	74·3 ± 5·1	69·8 ± 3·1	161 ± 4	163 ± 5	0·940 ± 0·005	0·900 ± 0·013	7·29 ± 0·02	7·19 ± 0·03
0·16	59·2 ± 4·3	53·9 ± 3·4	159 ± 3	153 ± 3	0·876 ± 0·014	0·836 ± 0·020	7·24 ± 0·01	7·23 ± 0·02
0·13	48·8 ± 2·5	40·6 ± 1·1	160 ± 5	162 ± 5	0·802 ± 0·024	0·668 ± 0·026	7·27 ± 0·02	7·21 ± 0·02
0·11	35·8 ± 2·1	32·3 ± 1·0	157 ± 3	168 ± 4	0·662 ± 0·029	0·538 ± 0·022	7·33 ± 0·03	7·24 ± 0·03

S, sedentary subjects; E, endurance-trained subjects; F_{I,O_2}, inspired O_2 fraction; P_{a,O_2}, arterialized oxygen partial pression; [Hb], blood haemoglobin concentration; S_{a,O_2}, arterial oxygen saturation; pH, arterialized blood pH. Data are given as means ± S.E.M.

Figure 1. Maximal oxygen consumption at various inspired oxygen fractions

$\dot{V}_{O_2,max}$ is maximal oxygen consumption. The data are normalized with respect to the value observed at an F_{I,O_2} of 0·30. F_{I,O_2} is inspired oxygen fraction. ●, sedentary subjects (S); ○, endurance-trained subjects (E). Bars indicate S.E.M.
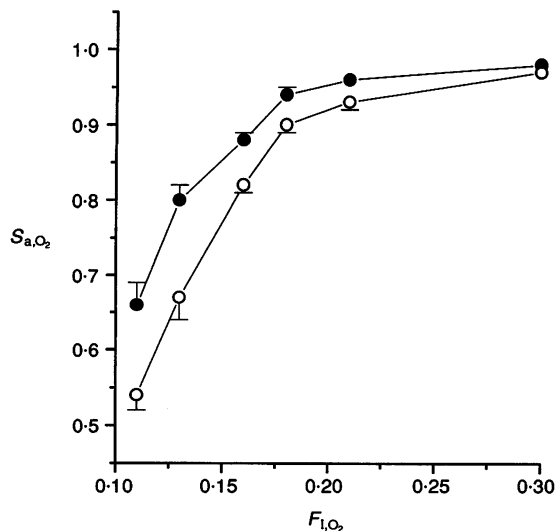
Figure 2. Arterial oxygen saturation at various inspired oxygen fractions

S_{a,O_2}, arterial oxygen saturation. ●, sedentary subjects (S); O, endurance-trained subjects (E). Bars indicate s.e.m.

so that the two curves tended to converge in hypoxia. In fact, the $\dot{V}_{O_2,max}$ of S was on average 23 and 13% lower than that of E in normoxia and at an F_{I,O_2} of 0·11, respectively. Similarly, the mechanical power at maximal exercise was greater in E than in S, and it increased more in E than in S for a given rise of F_{I,O_2}. As a consequence, the mean power difference between the two groups at maximal exercise was 100 W in normoxia, but only 50 W at the lowest F_{I,O_2}. Maximal [La]$_b$ was independent of F_{I,O_2}, and did not differ significantly between the two groups, despite a tendency towards higher [La]$_b$ values in E than in S. Accordingly, arterialized blood pH at maximal exercise was significantly lower in E than in S (Table 2).

Normalized $\dot{V}_{O_2,max}$ and S_{a,O_2} were plotted as a function of F_{I,O_2}, for both S and E, in Figs 1 and 2, respectively. Both parameters showed a non-linear increase with F_{I,O_2}. With the obvious exception of hyperoxia, both normalized $\dot{V}_{O_2,max}$ (Fig. 1) and S_{a,O_2} (Fig. 2) were systematically higher in S than in E ($P < 0·05$ and $P < 0·01$, respectively). For both parameters, the difference became wider as F_{I,O_2} was lowered. Similarly, P_{a,O_2} increased with F_{I,O_2} in both groups,

and at any F_{I,O_2} it was slightly, although non-significantly, lower in E than in S (Table 2).

The relationships between normalized $\dot{V}_{O_2,max}$ and F_{I,O_2} were strikingly similar to those between S_{a,O_2} and F_{I,O_2}. Accordingly, no difference was found when normalized $\dot{V}_{O_2,max}$ was compared with S_{a,O_2} within each group. Normalized $\dot{V}_{O_2,max}$ was plotted as a function of S_{a,O_2} in Fig. 3. The resulting linear relationships for E and S were not significantly different from each other ($P > 0·05$ for both coincidence and parallelism).

DISCUSSION

The decrease of $\dot{V}_{O_2,max}$ in acute hypoxia in S, as found in this study, is in good agreement with previous reports (Cerretelli, 1980; Ward et al. 1989; Ferretti, 1990; Cerretelli & Hoppeler, 1996). The slope of the curve increased with lowering F_{I,O_2}. The curve relating normalized $\dot{V}_{O_2,max}$ to F_{I,O_2} in E, although of the same shape as that for S, was displaced below that for S. The difference between the two curves was enlarged by hypoxia. These results agree with and complete
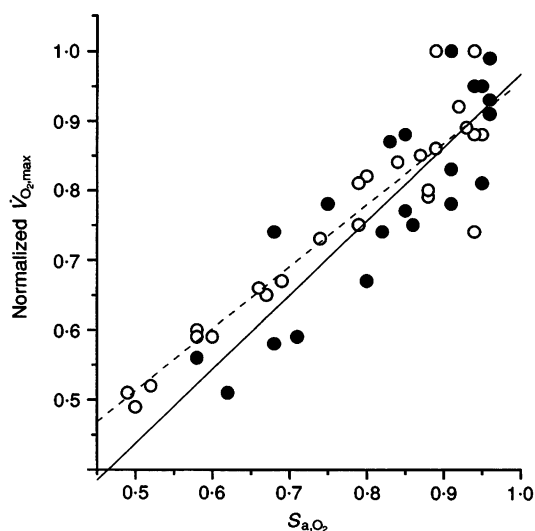

Figure 3. Maximal oxygen consumption as a function of arterial oxygen saturation

The $\dot{V}_{O_2,max}$ data are normalized with respect to the value observed at an F_{I,O_2} of 0·30. ● and continuous line, sedentary subjects (S). O and dashed line, endurance-trained subjects (E). Regression equations are as follows: sedentary subjects; $y = 1·059x - 0·091$, $n = 21$, correlation coefficient $r = 0·871$, $P < 0·0001$; endurance-trained subjects; $y = 0·886x + 0·070$, $n = 25$, $r = 0·930$, $P < 0·0001$.

previous observations by others, who reported a negative relationship between individual normoxic $\dot{V}_{O_2,max}$ and the decrease in $\dot{V}_{O_2,max}$ at one given level of acute hypoxia (Terrados *et al.* 1985; Lawler *et al.* 1988). Indeed, this study reports the first systematic comparison of $\dot{V}_{O_2,max}$ between E and S at several levels of hypoxia.

The observation that in both groups normalized $\dot{V}_{O_2,max}$ was not significantly different from S_{a,O_2} suggests that the relationships between either $\dot{V}_{O_2,max}$ or S_{a,O_2} and F_{I,O_2} may indeed reflect the same phenomenon, namely the blood oxygen equilibrium curve, those curves being a mirror image of this. If it is so, the relationships between normalized $\dot{V}_{O_2,max}$ and S_{a,O_2} for E and S must not only be linear, as already reported for S (Stenberg Ekblom & Messin, 1966; Squires & Buskirk, 1982), but also equal. This was indeed the case, as indicated by a comparison of the lines shown in Fig. 3.

The present results appear thus to support the tested hypothesis that the the shape of the relationship between $\dot{V}_{O_2,max}$ and P_{I,O_2} (or F_{I,O_2}) is imposed by the shape of the oxygen equilibrium curve. The slope of the $\dot{V}_{O_2,max}$ *vs.* P_{I,O_2} relationship, which is equal to the overall conductance to oxygen flow, increases as P_{I,O_2} drops. This obviously implies that an increase in conductance (or decrease of its reciprocal, the resistance) at some site along the oxygen transfer system must occur in hypoxia. The cardiovascular conductance to oxygen flow (G_Q) may be responsible for such a change, as a consequence of the sigmoid shape of the oxygen equilibrium curve (Piiper & Scheid, 1981; Ferretti & di Prampero, 1995). In fact G_Q is the product of cardiac output times the oxygen transport coefficient of blood (βb). The latter, which is equal to:

$$\beta b = \frac{(C_{a,O_2} - C_{\bar{v},O_2})}{(P_{a,O_2} - P_{\bar{v},O_2})}, \qquad (1)$$

where C_{a,O_2}, $C_{\bar{v},O_2}$, P_{a,O_2} and $P_{\bar{v},O_2}$ are the concentrations (C) or the partial pressures (P) of oxygen in arterial (a) or mixed venous (v̄) blood, is nothing but the mean slope of the oxygen equilibrium curve. In hypoxia, the decrease in P_{I,O_2}, and thus in P_{a,O_2}, is not accompanied by a corresponding decrease in C_{a,O_2} until the steep quasi-linear part of the oxygen equilibrium curve is attained. According to eqn (1), this implies an increase in βb, and thus in G_Q, in moderate hypoxia. Of course the same reasoning would apply to hyperoxia: in fact even a marked increase in P_{I,O_2} can induce only small changes in $\dot{V}_{O_2,max}$ (Bannister & Cunningham, 1954; Margaria, Cerretelli, Marchi & Rossi, 1961; Margaria, Camporesi, Aghemo & Sassi, 1972; Fagraeus, Karlsson, Linnarsson & Saltin, 1973; Welch & Pedersen, 1981), because P_{a,O_2} is on the flat part of the oxygen equilibrium curve, so that C_{a,O_2} cannot increase, with consequent decrease in βb, and thus in G_Q.

In this context, based on blood oxygenation and P_{a,O_2}, endurance athletes, with elevated individual $\dot{V}_{O_2,max}$ values, and with a reduced S_{a,O_2} at maximal exercise in normoxia

(Dempsey *et al.* 1984; Williams *et al.* 1986; Powers *et al.* 1989), undergo a greater decrease of $\dot{V}_{O_2,max}$ in hypoxia than sedentary individuals, because they have only small margins for increasing G_Q in hypoxia, as they operate on a different position on the oxygen equilibrium curve from the non-athletic subjects. Their normoxic P_{a,O_2} values are in fact already near the steep part of this curve, so that the overall resistance to oxygen flow cannot decrease in E as much as in S, and the oxygen transfer system of the former tends toward 'linearity'. As a consequence, the $\dot{V}_{O_2,max}$ of E in hypoxia cannot be maintained elevated in spite of the drops of P_{I,O_2} and P_{a,O_2}, as occurs in S. Furthermore, at maximal exercise, the physiological oxygen equilibrium curve of E might have been displaced to the right with respect to that for S. This is suggested by the lower pH in the former than in the latter group, and may have further contributed to arterial oxygen desaturation and to the 'linearization' of the $\dot{V}_{O_2,max}$ decrease in hypoxia observed in E.

The preceding argument relies on the assumption that the maximal cardiac output is unchanged in hypoxia with respect to normoxia. This assumption has got experimental support in acute normobaric hypoxia (Stenberg *et al.* 1966; Hartley, Vogel & Landowne, 1973; Ekblom, Huot, Stein & Thorstensson, 1975), which is the condition prevailing in the present study, but not in chronic hypobaric hypoxia, such as after altitude acclimatization (Pugh, 1964; Cerretelli, 1976). In the latter case maximal cardiac output is reduced, so that the decrease of $\dot{V}_{O_2,max}$ in hypoxia may be greater than that of S_{a,O_2}, as suggested by West *et al.* (1983), even though the shape of the oxygen equilibrium curve may determine the non-linear decrease of $\dot{V}_{O_2,max}$ also in chronic hypobaric hypoxia. This is suggested by the observation of a greater decrease in $\dot{V}_{O_2,max}$ in athletic than in non-athletic individuals also in this condition (Young *et al.* 1985). However, the shape of the $\dot{V}_{O_2,max}$ *vs.* P_{I,O_2} relationship in chronic hypobaric hypoxia is almost identical to that in acute normobaric hypoxia (Cerretelli, 1980; Ferretti, 1990; Cerretelli & Hoppeler, 1996), in apparent contrast with the preceding argument. This may be the result of ventilatory acclimatization in chronic hypoxia (Rahn & Otis, 1949; West, 1988), which may counteract the negative effects on $\dot{V}_{O_2,max}$ of a lower cardiac output at maximal exercise. Indeed the role of ventilatory resistances to oxygen flow in limiting $\dot{V}_{O_2,max}$ appears to increase in hypoxia (Ferretti & di Prampero, 1995).

The present results have some practical implications for extreme human performances. After the top of Mount Everest was reached for the first time without supplementary oxygen, it was assumed that this had been possible because the climbers had an extremely high $\dot{V}_{O_2,max}$. However, this is not so (West *et al.* 1983; Oelz *et al.* 1986). The present results demonstrate that very high $\dot{V}_{O_2,max}$ values in normoxia are not required for extreme altitude climbing, since this would be accompanied by a relatively great decrease of $\dot{V}_{O_2,max}$ in hypoxia. By the same token, on the assumption that the decrease of $\dot{V}_{O_2,max}$ in hypoxia would be

the same in E as in S, it was predicted that the optimal altitude for top performances in cycling would be 3600 m (di Prampero, Cortili, Mognoni & Saibene, 1979). This prediction was never confirmed by actual athletic performances. The two athletes, who established world records at sea level and at altitude in comparable technical conditions, obtained worse performances at altitude than previously predicted, in good agreement with the present results.

The results of this study have no direct implications with regard to $\dot{V}_{O_2,max}$ limitation. They provide a possible explanation for the shape of the relationship between $\dot{V}_{O_2,max}$ and F_{I,O_2} or P_{I,O_2}, independent of the interrelations among the various in-series resistances which set out the fractional limitation of $\dot{V}_{O_2,max}$ at any given F_{I,O_2}. What is relevant in the present context is that the intrinsic variability of the cardiovascular conductance to oxygen flow is sufficient to explain how $\dot{V}_{O_2,max}$ varies in hypoxia or in hyperoxia. In order to perform a quantitative analysis of the factors which limit $\dot{V}_{O_2,max}$ in the different conditions tested in this study, one should induce, at any given constant P_{I,O_2}, independent variations in one specific resistance/conductance and then describe the ensuing changes in $\dot{V}_{O_2,max}$ (Ferretti & di Prampero, 1995). This was not done in the present experiments.

In conclusion, the results of this study are compatible with the hypothesis that the relationship between $\dot{V}_{O_2,max}$ and P_{I,O_2} is a faithful reflection of the oxygen equilibrium curve. This being the case, the decrease of $\dot{V}_{O_2,max}$ in hypoxia is greater in endurance athletes than in non-athletic subjects, because they operate on different positions on the oxygen equilibrium curve, the S_{a,O_2} at maximal exercise in normoxia and at any level of hypoxia being lower in the former than in the latter group.

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