The effects of breathing He–O_2 mixtures on maximal oxygen consumption in normoxic and hypoxic men

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1. The hypothesis that the ventilatory resistance to O_2 flow (R_V) does limit maximal O_2 consumption ($\dot{V}_{O_2,max}$) in hypoxia, but not in normoxia, at least in non-athletic subjects, was tested. R_V was reduced by using He–O_2 mixtures.

2. $\dot{V}_{O_2,max}$ was measured during graded cyclo-ergometric exercise in eight men (aged 30 ± 3 years) who breathed N_2–O_2 and He–O_2 mixtures in normoxia (inspired oxygen fraction (F_{I,O_2}) = 0·21) and hypoxia (F_{I,O_2} = 0·11). O_2 consumption, expired and alveolar ventilations ($\dot{V}_E$ and $\dot{V}_A$, respectively), blood lactate and haemoglobin concentrations, heart rate and arterial oxygen saturation (S_{a,O_2}) were determined at the steady state of each work load. Arterial O_2 and CO_2 partial pressures (P_{a,O_2} and P_{a,CO_2}, respectively) were measured at rest and at the end of the highest work load.

3. Maximal $\dot{V}_E$ and $\dot{V}_A$ were significantly increased by He–O_2 breathing in normoxia (+27 and +18%, respectively), without significant changes in P_{a,O_2}, S_{a,O_2} and $\dot{V}_{O_2,max}$. In hypoxia, $\dot{V}_E$ and $\dot{V}_A$ increased (+31 and +24%, respectively), together with P_{a,O_2} (+17%), S_{a,O_2} (+6%) and $\dot{V}_{O_2,max}$ (+14%).

4. The results support the hypothesis that the role of R_V in limiting $\dot{V}_{O_2,max}$ is negligible in normoxia. In hypoxia, the finding that higher $\dot{V}_E$ and $\dot{V}_A$ values during He–O_2 breathing led to higher $\dot{V}_{O_2,max}$ values suggests a greater role of R_V as a limiting factor. It is unclear whether the finding that the $\dot{V}_{O_2,max}$ values were the same during He–O_2 and N_2–O_2 breathing in normoxia is due to a non-linear response of the O_2 transfer system, as previously proposed.

In recent years, multifactorial models of maximal O_2 consumption ($\dot{V}_{O_2,max}$) limitation have been gaining momentum against the classical unifactorial view that in normoxic man $\dot{V}_{O_2,max}$ is limited only by cardiovascular O_2 transport, at least during exercises involving large muscle groups (Clausen, 1977; Blomqvist & Saltin, 1983; Ekblom, 1986). On one side, Wagner (1992, 1993) has looked at a two-site system (perfusion *vs.* diffusion) and stressed the role of peripheral O_2 diffusion as a limiting factor. On the other side, a quantitative model of $\dot{V}_{O_2,max}$ limitation has been proposed (di Prampero, 1985; di Prampero & Ferretti, 1990), on the assumption that the flow of O_2 from ambient air to mitochondria is driven by pressure gradients across a cascade of resistances in-series. Each resistance to O_2 flow is considered to provide a given measurable fraction of the overall $\dot{V}_{O_2,max}$ limitation. Application of this model leads to the conclusion that cardiovascular O_2 transport imposes most of the limits to $\dot{V}_{O_2,max}$ (60–70%), whereas the role of pulmonary ventilation and gas exchange appears negligible, at least in healthy non-athletic subjects in normoxia (di Prampero & Ferretti, 1990; Turner *et al.* 1993; Ferretti & di Prampero, 1995).

The latter statement relies on the postulate that in normoxia any change in the ventilatory resistance (R_V) would be counteracted by an equivalent opposite change in the cardiovascular resistance (R_Q), due to the shape of the O_2 equilibrium curve. In fact, higher alveolar ventilation ($\dot{V}_A$) would lead to an increase in alveolar O_2 partial pressure (P_{A,O_2}) and probably in arterial O_2 partial pressure (P_{a,O_2}). Any increase in P_{a,O_2}, however, cannot be accompanied by a concurrent increase in arterial O_2 concentration (C_{a,O_2}), because it occurs on the flat part of the O_2 equilibrium curve. This implies a decrease in the oxygen transport coefficient in the blood phase, β_b, which is equal to:

$$\beta_b = (C_{a,O_2} - C_{\bar{v},O_2})/(P_{a,O_2} - P_{\bar{v},O_2}), \quad (1)$$

where $C_{\bar{v},O_2}$ is mixed venous O_2 concentration and $P_{\bar{v},O_2}$ is mixed venous O_2 partial pressure. Since $R_Q = \dot{Q}^{-1}\beta_b^{-1}$, where $\dot{Q}$ is cardiac output, this necessarily implies an increase in R_Q. In contrast, in hypoxia any increase in $\dot{V}_A$, and

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subsequently in P_{A,O_2} and P_{a,O_2}, would also lead to a significant increase in C_{a,O_2}, since the P_{a,O_2} values lie on the steep part of the O_2 equilibrium curve. As a consequence, the postulated compensation through changes in R_Q cannot operate, and $\dot{V}_{O_2,max}$ can vary as a function of R_V.

This topic was examined by Ferretti & di Prampero (1995), who simulated the effects of independent changes in R_V on $\dot{V}_{O_2,max}$ in normoxia and in hypoxia. The results showed that R_V provides less than 5% of the $\dot{V}_{O_2,max}$ limitation in normoxia. In hypoxia, it appeared that the lower the inspired O_2 partial pressure (P_{I,O_2}), the greater the contribution of R_V to $\dot{V}_{O_2,max}$ limitation. If this is the case, the lower the P_{I,O_2} and thus P_{a,O_2}, the greater the effects of a reduction in R_V on $\dot{V}_{O_2,max}$.

Such a reduction can be achieved, for instance, by breathing low-density gas mixtures, such as He–O_2. In fact in the horse, He–O_2 breathing had no effect on $\dot{V}_{O_2,max}$ in normoxia (Erickson *et al.* 1994), but increased (Erickson *et al.* 1995) $\dot{V}_{O_2,max}$ in hypoxia . As far as humans are concerned, He–O_2 breathing has been reported to increase (Robertson & McRae, 1966; Brice & Welch, 1983), decrease (Murphy, Clark, Buckingham & Young, 1969; Spitler, Horvath, Kobayashi & Wagner, 1980) or have no effects (Bowers & Fox, 1967) on $\dot{V}_{O_2,max}$ in normoxia. No previous studies, to our knowledge, have investigated the effects of He–O_2 breathing on $\dot{V}_{O_2,max}$ in humans exposed to acute hypoxia.

The aim of the present study was to test the hypothesis that the role played by pulmonary ventilation in limiting $\dot{V}_{O_2,max}$ is negligible in normoxia, at least in healthy non-athletic subjects, but is noticeable in hypoxia. To this purpose, R_V was specifically reduced by administering He–O_2 gas mixtures during exercise, and $\dot{V}_{O_2,max}$ was measured in normoxia and in hypoxia.

METHODS

Subjects

After approval by the local ethical committee, eight male non-athletic subjects (age, 30 ± 3 years; mean ± S.E.M.) were admitted to this study. All subjects gave written informed consent. They were all clinically healthy and had a normal resting and exercise electrocardiogram. None of them were involved in a specific training programme nor underwent prolonged altitude exposure during the six months preceding this study.

Methods

The O_2 consumption at the exercise steady state ($\dot{V}_{O_2}$) was measured by the standard open circuit method. During N_2–O_2 breathing, expired gas was collected into Douglas bags, and its volume was determined by means of a dry gas meter (Singer DTM 15; USA). During He–O_2 breathing, expired air was collected into an 80 l Tissot spirometer, which had previously been re-equilibrated for the use of He–O_2 mixtures. Expired O_2 and CO_2 fractions were measured by a paramagnetic O_2 analyser (Oxynos 1-C; Leybold Haereus, Hanau, Germany) and an infrared CO_2 analyser (LB-2; Leybold Haereus), respectively. The gas analysers were calibrated with gas mixtures of known composition, balanced with either N_2 or He. $\dot{V}_{O_2}$ was computed by a standard procedure. CO_2 output, expired ventilation ($\dot{V}_E$) and the gas exchange ratio (R) were also calculated.

Blood lactate concentration ($[La]_b$) was measured by an electroenzymatic method (ESAT 6661 Lactat; Eppendorf, Hamburg, Germany) on 20 μl blood samples from an ear lobe. Heart rate (f_H) was measured continuously by electrocardiography (ETM 2000; Elmed, Augsburg, Germany). Arterial O_2 saturation (S_{a,O_2}) was measured continuously by finger-tip infrared oxymetry (Pulsox-5; Minolta, Japan). Haemoglobin concentration ([Hb]) was determined by a standard photometric technique (B-Hemoglobin, Hemocue AB, Angelholm, Sweden) on 10 μl ear lobe blood samples. Arterial blood pH, P_{a,O_2} and arterial CO_2 partial pressure (P_{a,CO_2}) were measured by means of microelectrodes (Ciba Corning 280 blood gas system, Medfield, MA, USA) on 80 μl arterialized blood samples from an ear lobe. $\dot{V}_A$ was then calculated from the Bohr equation, assuming that P_{A,CO_2} was equal to P_{a,CO_2}.

Exercise testing protocol

$\dot{V}_{O_2,max}$ was determined during graded exercise on the cycle ergometer. Each submaximal work load lasted 5 min. The lowest powers were 50 and 100 W for hypoxic and normoxic conditions, respectively. Power was then progressively increased by 50 W steps. The step increase was reduced to 25 W as the individual maximum was approached. $\dot{V}_{O_2}$ was determined during the last minute of each work load. Successive work loads were separated by 5 min recovery intervals, during which blood samples were taken at 1, 3 and 5 min for the determination of $[La]_b$. At rest prior to exercise and immediately after the end of the highest work load, arterialized blood samples were obtained from the ear lobe and immediately analysed.

The individual $\dot{V}_{O_2,max}$ was established from the plateau attained by the relationship between oxygen uptake and mechanical power above a given power. When the plateau was not evident, the following criteria for establishing $\dot{V}_{O_2,max}$ were used: (i) the lack of increase in f_H between two successive work loads ($\Delta f_H <$ 5 beats min^{-1}), (ii) R values higher than 1·1, and (iii) $[La]_b$ higher than 10 mM. The minimum power requested at which $\dot{V}_{O_2}$ was equal to $\dot{V}_{O_2,max}$ was defined as $\dot{W}_{max}$.

Four $\dot{V}_{O_2,max}$ measurements were carried out. The first was always in ambient air (normoxia, $P_{I,O_2} = 150$ Torr). The other tests were performed while the subjects breathed either a N_2–O_2 mixture with an inspired O_2 fraction, F_{I,O_2}, of 0·11 ($P_{I,O_2} = 80$ Torr) or He–O_2 mixtures with F_{I,O_2} of 0·21 and 0·11 in a random order. Successive tests were separated by at least 2 days to avoid specific training effects. Except for ambient air, inspired gas was provided by a cylinder, and was administered via a Douglas bag acting as a volume buffer, through a 2·5 cm diameter hose. The length of the hose was 2·8 and 1·8 m for He–O_2 and N_2–O_2 breathing, respectively, in order to minimize differences in resistance along the hose between the two conditions. F_{I,O_2} at the entrance of the valve was continuously monitored. Ten minutes at rest were allowed for equilibration, before the exercise test was carried out.

Statistical analysis

Data are reported as means ± S.E.M. A two-way ANOVA for repeated measurements was used for statistical analysis. When significant interactions were found, a *post hoc* test (Tukey's test) was then applied for evaluation of the effect of He–O_2 breathing, both in normoxia and in hypoxia. Linear relationships were studied by regression analysis. The results were considered significant if $P < 0·05$.

Table 1. Mean values (± S.E.M.) of the measured and calculated variables in the four tested conditions at maximal exercise

	$\dot{V}_{O_2,max}$ (l min^{-1})	$\dot{V}_{O_2,max}$ (ml min^{-1} kg^{-1})	R	$\dot{W}_{max}$ (W)	$\dot{V}_E$ BTPS (l min^{-1})	$\dot{V}_A$ BTPS (l min^{-1})	f_H (beats min^{-1})	$[La]_b$ (mM)
Normoxia								
N_2–O_2	2·99 ± 0·26	43·9 ± 3·5	1·19 ± 0·06	236·3 ± 17·4	109·9 ± 5·8	95·1 ± 6·6	186·0 ± 1·6	11·1 ± 0·6
He–O_2	3·07 ± 0·27	45·2 ± 3·7	1·20 ± 0·04	242·6 ± 16·4	139·1 ± 14·2*	112·1 ± 11·0	186·0 ± 2·1	11·4 ± 0·8
Hypoxia								
N_2–O_2	1·96 ± 0·09	28·7 ± 1·4	1·23 ± 0·05	156·4 ± 9·9	107·8 ± 8·8	82·1 ± 7·4	176·9 ± 3·3	11·2 ± 0·9
He–O_2	2·23 ± 0·16*	32·6 ± 2·3*	1·24 ± 0·03	183·6 ± 14·4*	141·3 ± 13·3*	101·5 ± 10·6*	180·3 ± 3·0	11·7 ± 1·0

$\dot{V}_{O_2,max}$, maximal oxygen consumption; R, respiratory exchange ratio; $\dot{W}_{max}$, minimum power for which O_2 consumption is equal to $\dot{V}_{O_2,max}$; $\dot{V}_E$, expired ventilation; $\dot{V}_A$, alveolar ventilation; BTPS, body temperature and pressure, saturated; f_H, heart rate; $[La]_b$, blood lactate concentration. * $P < 0·05$ compared with N_2 breathing.

RESULTS

Submaximal exercise

All submaximal 5 min work loads could be completed by all the subjects. At any work load, the same submaximal $\dot{V}_{O_2}$ values were observed with He–O_2 and N_2–O_2 breathing, whether in normoxia or in hypoxia. Thus, as appears from Fig. 1, the relationships between the corresponding $\dot{V}_{O_2}$ values in He–O_2 and N_2–O_2 were not significantly different from the identity line. This allowed the establishment of an overall linear relationship between $\dot{V}_{O_2}$ and power, independent of F_{I,O_2} and breathed gas mixtures. This relationship (not shown in a figure) is described by the equation: $\dot{V}_{O_2} = 0·307 + 0·011\ \dot{W}$ ($\dot{W}$ being power, in W; $n = 128$; adjusted $r^2 = 0·95$; $P < 0·001$), from which an average mechanical efficiency of exercise of 0·25 was obtained.

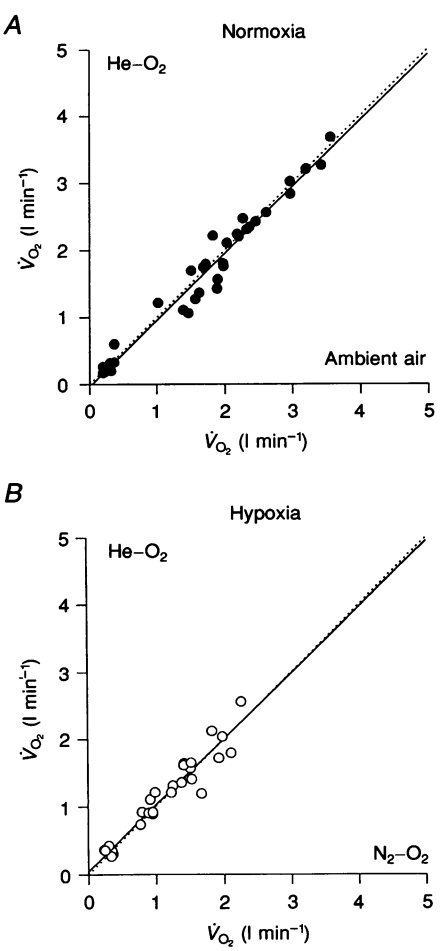

Figure 1. Oxygen consumption during He–O_2 and N_2–O_2 breathing at submaximal exercise

Oxygen consumption ($\dot{V}_{O_2}$) during He–O_2 breathing as a function of $\dot{V}_{O_2}$ during N_2–O_2 breathing in normoxia (*A*) and in hypoxia (*B*). The regression lines (continuous lines; $y = -0·03 + 0·99x$, $r^2 = 0·97$, $P < 0·001$; and $y = 0·04 + 0·98x$, $r^2 = 0·93$, $P < 0·001$; for normoxia and hypoxia, respectively) are not significantly different from the identity lines (dotted lines).

Table 2. Mean values (± S.E.M.) of arterial blood parameters in the four tested conditions at maximal exercise

	[Hb] ($g\ l^{-1}$)	S_{a,O_2}	P_{a,O_2} (Torr)	pH	P_{a,CO_2} (Torr)
Normoxia					
N_2–O_2	173·1 ± 5·7	0·95 ± 0·01	86·5 ± 0·3	7·29 ± 0·01	29·9 ± 1·1
He–O_2	171·5 ± 3·4	0·96 ± 0·00	85·4 ± 1·2	7·28 ± 0·02	27·3 ± 1·8
Hypoxia					
N_2–O_2	169·9 ± 3·6	0·66 ± 0·02	40·0 ± 2·2	7·32 ± 0·03	27·4 ± 1·7
He–O_2	170·3 ± 2·5	0·70 ± 0·02*	46·6 ± 1·9*	7·30 ± 0·03	24·7 ± 1·4*

[Hb], haemoglobin concentration; S_{a,O_2}, arterial O_2 saturation; P_{a,O_2}, arterial O_2 partial pressure; pH, arterial pH; P_{a,CO_2}, arterial CO_2 partial pressure. * $P < 0·05$ compared with N_2 breathing.

Similarly, the same submaximal $\dot{V}_E$ values were observed at each work load during He–O_2 and N_2–O_2 breathing, both in normoxia and hypoxia. Thus, the relationships between the corresponding $\dot{V}_E$ values in He–O_2 and N_2–O_2 (Fig. 2) were not significantly different from the identity line. This indicates that the ventilatory equivalent was unaffected by helium breathing.

Maximal exercise

The measured and calculated metabolic variables at maximal exercise during the four experimental conditions are shown in Table 1. The corresponding blood O_2 transport parameters and blood pH data are shown in Table 2. Figure 3 shows the percentage gain in $\dot{V}_{O_2,max}$, $\dot{W}_{max}$, $\dot{V}_E$, $\dot{V}_A$ and S_{a,O_2} induced by replacing N_2 with He, in normoxia and

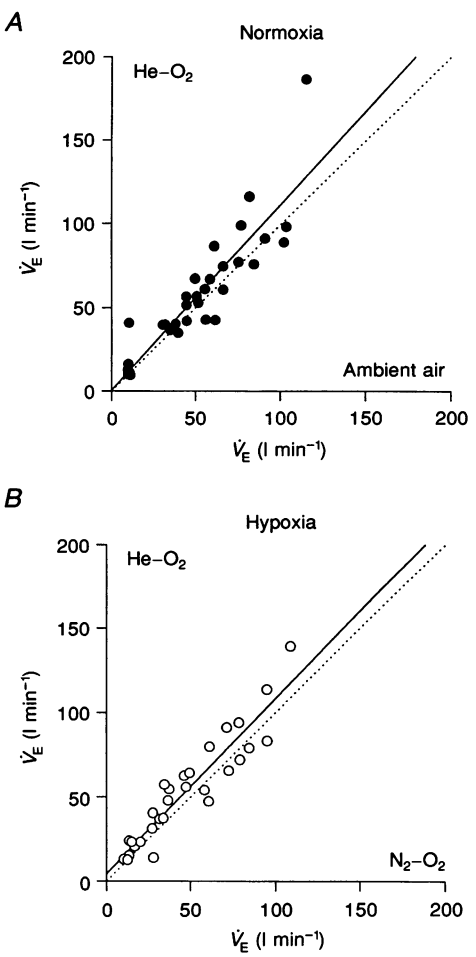

Figure 2. Pulmonary ventilation during He–O_2 and N_2–O_2 breathing at submaximal exercise

Expired ventilation ($\dot{V}_E$) during He–O_2 breathing as a function of $\dot{V}_E$ during N_2–O_2 breathing in normoxia (*A*) and in hypoxia (*B*). The regression lines (continuous lines; $y = 0·51 + 1·12x$, $r^2 = 0·81$, $P < 0·001$; and $y = 4·5 + 1·04x$, $r^2 = 0·87$, $P < 0·001$; for normoxia and hypoxia, respectively) are not significantly different from the identity lines (dotted lines).

hypoxia, respectively. In normoxia, $\dot{V}_E$ (+27 ± 8%) and $\dot{V}_A$ (+18 ± 7%) increased significantly without any change in $\dot{V}_{O_2,max}$ (+3 ± 2%, n.s. (not significant)). In contrast, in hypoxia, the significantly higher $\dot{V}_E$ (+31 ± 9%) and $\dot{V}_A$ (+24 ± 9%) values were accompanied by a significant increase in $\dot{V}_{O_2,max}$ (+14 ± 4%). The variations in $\dot{V}_{O_2,max}$ were paralleled by the changes in mechanical power (+3 ± 2%, n.s.; and +17 ± 2% in normoxia and hypoxia, respectively).

The increases in $\dot{V}_E$ and $\dot{V}_A$ were associated with a drop in P_{a,CO_2}, which was significant in hypoxia (−10 ± 4%), but not in normoxia (−9 ± 6%). At maximal exercise R, $[La]_b$, [Hb] and f_H were the same in normoxia and in hypoxia. S_{a,O_2} and P_{a,O_2} were significantly higher during He–O_2 than during N_2–O_2 breathing (+6 ± 2 and +17 ± 5%, respectively) in hypoxia. This was not the case for normoxia.

DISCUSSION

The reduction in the ventilatory resistance to O_2 flow

The reduction in R_V induced by He–O_2 breathing can be related to the combined effects of lower density and higher viscosity of He with respect to N_2 (Murphy *et al.* 1969; Papamoschou, 1995). At a given Reynolds number, all other variables being constant, gas flow is inversely proportional to the ratio of inertial to viscous forces. Since the density of He is about 7 times lower and its viscosity 8% higher than that of N_2, higher gas flows occur at all Reynolds numbers when He–O_2 mixtures rather than N_2–O_2 mixtures are breathed. As a consequence: (i) the transition from laminar to turbulent flow takes place at higher flows in the former than in the latter case, and (ii) the respiratory unloading during He–O_2 breathing persists also under fully turbulent flow conditions.

For a given length, average diameter and pressure gradient of the airways, the gas flow ratio is given by (Papamoschou, 1995):

$$\frac{\dot{V}_{He-O_2}}{\dot{V}_{N_2-O_2}} \approx \sqrt{\frac{\rho f_{N_2-O_2}}{\rho f_{He-O_2}}}, \quad (2)$$

where ρ is the gas density and f the friction factor. Under conditions of turbulent flow, f is constant, and the increase in gas flow during He–O_2 breathing can be predicted from ρ changes only. Assuming that air flow at maximal exercise is turbulent in most of the airways, it can be calculated that $\dot{V}_E$ should increase by approximately 70 and 100% during He–O_2 breathing in normoxia and hypoxia, respectively. In contrast to this prediction, $\dot{V}_E$ was 27 and 31% and $\dot{V}_A$ was 18 and 24% higher during He–O_2 than N_2–O_2 breathing in normoxia and hypoxia, respectively, i.e. less than expected on a merely physical basis. These findings in normoxia are in good agreement with previous reports at maximal exercise (Wilson & Welch, 1980; Brice & Welch, 1983), although other investigators (Spitler *et al.* 1980) observed a lower increase in $\dot{V}_E$ during He–O_2 breathing. Three factors may explain this apparent discrepancy. Firstly, transitional and turbulent flows are attained at ~3 times higher flows in He–O_2 than in N_2–O_2. Thus turbulent flow would appear in a smaller fraction of the airways and for a shorter time during a respiratory cycle in the former than in the latter

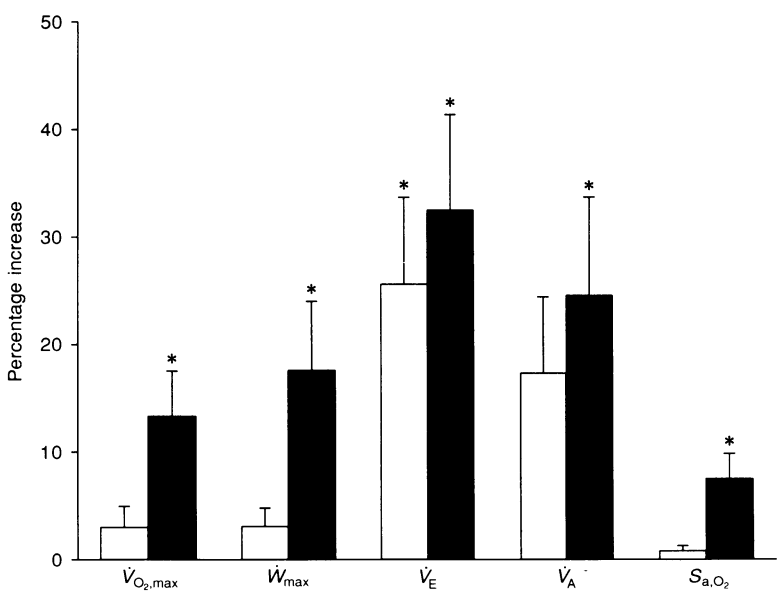

Figure 3. Percentage changes in mechanical and respiratory variables at maximal exercise during He–O_2 breathing

Percentage increase in maximal O_2 consumption ($\dot{V}_{O_2,max}$), minimum power requiring an O_2 consumption equal to $\dot{V}_{O_2,max}$ ($\dot{W}_{max}$), expired ventilation ($\dot{V}_E$), alveolar ventilation ($\dot{V}_A$) and arterial O_2 saturation (S_{a,O_2}), induced by He–O_2 breathing in normoxia (□) and hypoxia (■). * $P < 0{\cdot}05$. Error bars are S.E.M.

case (Murphy *et al.* 1969). Secondly, mechanical limitation of exercise hyperpnoea, although barely apparent during maximal exercise in air (Olafsson & Hyatt, 1969; Younes & Kivinen, 1984), may prevent a greater increase in $\dot{V}_E$ than that observed in the present study. Finally, the hyperventilation induced by respiratory unloading is obviously accompanied by a reduction of P_{a,CO_2}. This, in turn, may inhibit central chemoreceptor activity, and thus depress the activity of the respiratory centres. The outcome would be a lower increase in $\dot{V}_E$ and $\dot{V}_A$ than predicted. These three mechanisms may also explain the finding of similar $\dot{V}_E$ values during N_2–O_2 and He–O_2 breathing at submaximal exercise (Fig. 2), in good agreement with other studies in normoxia (Bowers & Fox, 1967; Murphy *et al.* 1969; Brice & Welch, 1983).

Factors limiting maximal O_2 consumption after ventilatory unloading

The main finding of the present study is that the reduction in R_V induced by He–O_2 breathing resulted in a significant increase in $\dot{V}_{O_2,max}$ during hypoxic exercise. This was not the case in normoxia. The present results agree with those obtained by others in the horse (Erickson *et al.* 1994, 1995), and appear compatible with the tested hypothesis that the role played by pulmonary ventilation and the gas exchange system in limiting $\dot{V}_{O_2,max}$ is important in hypoxia, but negligible in normoxia.

The results of the present study can be interpreted by means of the multifactorial model of $\dot{V}_{O_2,max}$ limitation. As previously pointed out, this model is an application of the O_2 conductance equation to maximal exercise. As far as the ventilatory conductance to O_2 flow ($G_V = R_V^{-1}$) is concerned, ventilatory O_2 transfer is equal to:

$$\dot{V}_{O_2,max} = G_V(P_{I,O_2} - P_{A,O_2}) = \dot{V}_A\beta_g(P_{I,O_2} - P_{A,O_2}), \quad (3)$$

where β_g is the O_2 transfer coefficient in the gas phase. Since in standard conditions β_g is a constant (1·16 ml l^{-1} $Torr^{-1}$ at 37 °C; see Piiper, Dejours, Haab & Rahn, 1971), the increase in G_V in this study turns out to be equivalent to that in $\dot{V}_A$. A quantitative analysis of the ventilatory limitation to $\dot{V}_{O_2,max}$ can thus be attempted, on the assumption of a steady state for $\dot{V}_A$ and $\dot{V}_{O_2,max}$.

If one resistance to O_2 flow is specifically and independently modified and the resulting effect on $\dot{V}_{O_2,max}$ is looked at, the fractional limitation to $\dot{V}_{O_2,max}$ imposed by that resistance (F_i) is given by:

$$F_i = d(\dot{V}_{O_2,max}\ \text{ratio})/d(\Delta R_i/R_i), \quad (4)$$

where the $\dot{V}_{O_2,max}$ ratio is the $\dot{V}_{O_2,max}$ before, divided by the $\dot{V}_{O_2,max}$ after, an acute manoeuvre leading to a change in the resistance at stake, and the term $\Delta R_i/R_i$ is the induced relative change in the resistance at stake (di Prampero & Ferretti, 1990; Ferretti & di Prampero, 1995). The $\dot{V}_{O_2,max}$ ratio is plotted as a function of the relative changes in R_V in

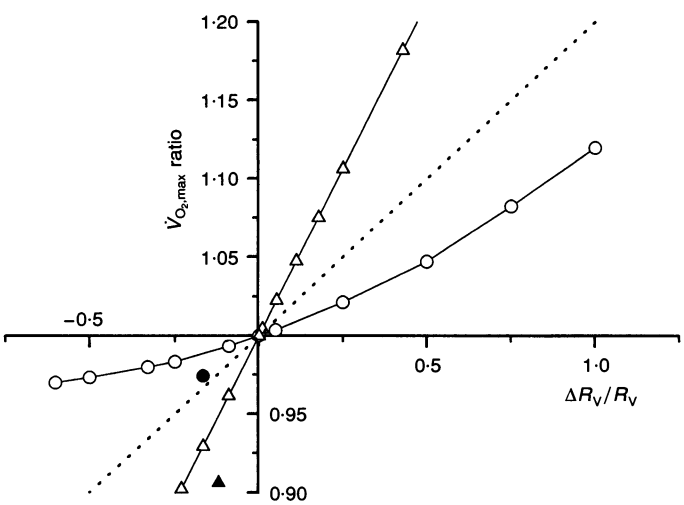

Figure 4. Effect of a change in ventilatory resistance to O_2 flow on maximal O_2 consumption

The changes in maximal O_2 consumption ($\dot{V}_{O_2,max}$) following the acute changes in the ventilatory resistance to O_2 flow (R_V), are presented on the y-axis as the ratio between the $\dot{V}_{O_2,max}$ before and the $\dot{V}_{O_2,max}$ after the ventilatory unloading. The relative changes in R_V, expressed as the R_V difference divided by the R_V before ventilatory unloading ($\Delta R_V/R_V$) are given on the x-axis. $\dot{V}_{O_2,max}$ ratios below 1 indicate an increase in $\dot{V}_{O_2,max}$ and $\Delta R_V/R_V$ values below 0 indicate a decrease in R_V. The continuous lines refer to the results of a simulation in normoxia (○; Ferretti & di Prampero, 1995) and hypoxia (inspired O_2 fraction of 0·11, △). The dashed line represents the relationship that would apply in the case of a linear O_2 transport system in normoxia (Ferretti & di Prampero, 1995). The slopes of these lines are equal to the fractional limitation to $\dot{V}_{O_2,max}$ imposed by R_V. The results of the present study are plotted as ● and ▲, for normoxia and hypoxia, respectively.

Fig. 4. As far as normoxia is concerned, two lines are shown, for a linear (dashed line) and non-linear (continuous line, ○) solution of the model, respectively (Ferretti & di Prampero, 1995). The point corresponding to the mean results of this study (●) is also given. The experimental point lies between the two lines, closer to that for a linear solution. This, associated with the lack of increase in P_{a,O_2} in normoxia, may undermine the argument of a compensatory increase in R_Q preventing $\dot{V}_{O_2,max}$ from changing. It is noteworthy, however, that for the decrease in R_V attained in this study, the average error of a $\dot{V}_{O_2,max}$ determination (Katch, Sady & Freedson, 1982; Howley, Bassett & Welch, 1995) does not allow discrimination between the linear and the non-linear solution of Fig. 4. Concerning hypoxia, the experimental point ▲ lies somewhat below the theoretical line (continuous line, △), suggesting a potential additional effect on a different resistance, perhaps related to pulmonary gas exchange.

In conclusion, the results of this study agree with the tested hypothesis that the lungs play a negligible role in limiting $\dot{V}_{O_2,max}$ in normoxia, at least in non-athletic subjects. Indeed, no significant changes in $\dot{V}_{O_2,max}$, despite the increase in $\dot{V}_E$ and $\dot{V}_A$ induced by breathing He–O_2 gas mixtures, were observed. In contrast, in hypoxia the induced increase in $\dot{V}_E$ and $\dot{V}_A$ was accompanied by significantly higher $\dot{V}_{O_2,max}$ values. This appears compatible with the hypothesis of a significant role of ventilation in limiting $\dot{V}_{O_2,max}$ in hypoxia. It remains unclear whether the lack of significant $\dot{V}_{O_2,max}$ changes during He–O_2 breathing in normoxia was an effect of a non-linear response of the O_2 transfer system, as proposed (di Prampero & Ferretti, 1990). Although the present data suggest that this may not be the case, greater changes in the ventilatory resistance to O_2 flow ought to be achieved to obtain a clear answer to this question.

Blomqvist, C. G. & Saltin, B. (1983). Cardiovascular adaptations to physical training. *Annual Review of Physiology* **45**, 169–189.

Bowers, R. W. & Fox, E. L. (1967). Metabolic and thermal responses of man in various He–O_2 and air environments. *Journal of Applied Physiology* **23**, 561–565.

Brice, A. G. & Welch, H. G. (1983). Metabolic and cardiorespiratory responses to He–O_2 breathing during exercise. *Journal of Applied Physiology* **54**, 387–392.

Clausen, J. P. (1977). Effect of physical training on cardiovascular adjustments to exercise in man. *Physiological Reviews* **57**, 779–815.

di Prampero, P. E. (1985). Metabolic and circulatory limitations to $\dot{V}_{O_2,max}$ at the whole animal level. *Journal of Experimental Biology* **115**, 319–331.

di Prampero, P. E. & Ferretti, G. (1990). Factors limiting maximal oxygen consumption in humans. *Respiration Physiology* **80**, 113–128.

Ekblom, B. (1986). Factors determining maximal aerobic power. *Acta Physiologica Scandinavica*, suppl. 556, 15–19.

Erickson, B. K., Seaman, J., Kubo, K., Hiraga, A., Kai, M., Yamaya, Y. & Wagner, P. D. (1994). Mechanism of reduction in alveolar–arterial P_{O_2} difference by helium breathing in the exercising horse. *Journal of Applied Physiology* **76**, 2794–2801.

Erickson, B. K., Seaman, J., Kubo, K., Hiraga, A., Kai, M., Yamaya, Y. & Wagner, P. D. (1995). Hypoxic helium breathing does not reduce alveolar–arterial P_{O_2} difference in the horse. *Respiration Physiology* **100**, 253–260.

Ferretti, G. & di Prampero, P. E. (1995). Factors limiting maximal O_2 consumption: effects of acute changes in ventilation. *Respiration Physiology* **99**, 259–271.

Howley, E. T., Bassett, D. R. Jr & Welch, H. G. (1995). Criteria for maximal oxygen uptake: review and commentary. *Medicine and Science in Sports and Exercise* **27**, 1292–1301.

Katch, V. L., Sady, S. S. & Freedson, P. (1982). Biological variability in maximum aerobic power. *Medicine and Science in Sports and Exercise* **14**, 21–25.

Murphy, T. M., Clark, W. H., Buckingham, I. P. B. & Young, W. A. (1969). Respiratory gas exchange in exercise during helium–oxygen breathing. *Journal of Applied Physiology* **26**, 303–307.

Olafsson, S. & Hyatt, R. E. (1969). Ventilatory mechanics and expiratory flow limitation during exercise in normal subjects. *Journal of Clinical Investigation* **48**, 564–573.

Papamoschou, D. (1995). Theoretical validation of the respiratory benefits of helium–oxygen mixtures. *Respiration Physiology* **99**, 183–190.

Piiper, J., Dejours, P., Haab, P. & Rahn, H. (1971). Concepts and basic quantities in gas exchange physiology. *Respiration Physiology* **13**, 292–304.

Robertson, W. G. & McRae, G. L. (1966). Study of man during a 56 day exposure to an O_2–He atmosphere at 258 mmHg total pressure; VI, Respiratory function. *Aerospace Medicine* **37**, 578–582.

Spitler, D. L., Horvath, S. M., Kobayashi, K. & Wagner, J. A. (1980). Work performance breathing normoxic nitrogen or helium gas mixtures. *European Journal of Applied Physiology* **43**, 157–166.

Turner, D. L., Hoppeler, H., Noti, C., Gurtner, H. P., Gerber, H., Schena, F., Kayser, B. & Ferretti, G. (1993). Limitations to $\dot{V}_{O_2,max}$ in humans after blood retransfusion. *Respiration Physiology* **92**, 329–341.

Wagner, P. D. (1992). Gas exchange and peripheral diffusion limitation. *Medicine and Science in Sports and Exercise* **24**, 54–58.

Wagner, P. D. (1993). Algebraic analysis of the determinants of $\dot{V}_{O_2,max}$. *Respiration Physiology* **93**, 221–237.

Wilson, G. D. & Welch, H. G. (1980). Effects of varying concentration of N_2/O_2 and He/O_2 on exercise tolerance in man. *Medicine and Science in Sports and Exercise* **12**, 380–384.

Younes, M. & Kivinen, G. (1984). Respiratory mechanics and breathing patterns during and following maximal exercise. *Journal of Applied Physiology* **57**, 1773–1782.

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