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ORIGINAL ARTICLE

Determinants of maximal oxygen uptake in moderate acute hypoxia in endurance athletes

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Abstract The factors determining maximal oxygen consumption were explored in eight endurance trained subjects (TS) and eight untrained subjects (US) exposed to moderate acute normobaric hypoxia. Subjects performed maximal incremental tests at sea level and simulated altitudes (1,000, 2,500, 4,500 m). Heart rate (HR), stroke volume (SV), cardiac output ($\dot{Q}$), arterialized oxygen saturation ($Sa'O_2$), oxygen uptake ($\dot{V}O_{2max}$), ventilation ($\dot{V}E$, expressed in normobaric conditions) were measured. At maximal exercise, ventilatory equivalent ($\dot{V}E/\dot{V}O_{2max}$), O_2 transport ($\dot{Q}aO_{2max}$) and O_2 extraction (O_2ER_{max}) were calculated. In TS, $\dot{Q}_{max}$ remained unchanged despite a significant reduction in HR_{max} at 4,500 m. SV_{max} remained unchanged. $\dot{V}E_{max}$ decreased in TS at 4,500 m, $\dot{V}E/\dot{V}O_{2max}$ was lower in TS and greater at 4,500 m vs. sea level in both groups. $Sa'O_{2max}$ decreased at and above 1,000 m in TS and 2,500 m in US, O_2ER_{max} increased at 4,500 m in both groups. $\dot{Q}aO_{2max}$ decreased with altitude and was greater in TS than US up to 2,500 m but not at 4,500 m. $\dot{V}O_{2max}$ decreased with altitude but the decrement ($\Delta\dot{V}O_{2max}$) was larger in TS at 4,500 m. In both groups $\Delta\dot{V}O_{2max}$ in moderate hypoxia was correlated with $\Delta\dot{Q}aO_{2max}$. Several differences between the two groups are probably responsible for the greater $\Delta\dot{V}O_{2max}$ in TS at 4,500 m : (1) the relative hypoventilation in TS as shown by the decrement in $\dot{V}E_{max}$ at 4,500 m (2) the greater $\dot{Q}aO_{2max}$ decrement in TS due to a lower $Sa'O_{2max}$ and unchanged $\dot{Q}_{max}$ 3) the smaller increase in O_2ER_{max} in TS, insufficient to compensate the decrease in $\dot{Q}aO_{2max}$.

Keywords Aerobic performance · Cardiac output · Arterial O_2 saturation · Venous O_2 saturation · Tissue O_2 extraction

Introduction

Significant decrements in maximal oxygen uptake ($\dot{V}O_{2max}$) have been consistently reported for individuals exposed to acute hypoxia when compared to sea level (Chapman et al. 1999; Ferretti et al. 1997; Gore et al. 1996; Lawler et al. 1988; Martin and O'Kroy 1993; Peltonen et al. 2001; Roberg et al. 1998; Squires and Buskirk 1982; Woorons et al. 2005). However, altitude does not appear to affect every individual in an equal manner. Some studies have shown that endurance trained athletes, compared with untrained individuals, demonstrate a larger decline in $\dot{V}O_{2max}$ at moderate altitudes (Chapman et al. 1999; Ferretti et al. 1997; Gore et al. 1993; Lawler et al. 1988; Woorons et al. 2005) and a lower threshold altitude where a significant decrease in $\dot{V}O_{2max}$ appears (Chapman et al. 1999; Gore et al. 1993; Terrados et al. 1985). This particular sensitivity of athletes to hypoxia has been related to an important decrease in arterial saturation (SaO_2) (Gore et al. 1993; Lawler et al. 1988; Woorons et al. 2005). In normoxia, exercise induced arterial O_2 desaturation is defined as a $\%SaO_2$ of less than or equal to 92% during maximal exercise (Powers et al. 1988). This arterial O_2 desaturation, which exists in normoxia mainly in highly trained endurance athletes (Dempsey et al. 1982),

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is mostly important in acute hypoxia because the impairment in pulmonary gas exchange is accentuated, particularly in subjects with a high $\dot{V}O_{2max}$ (Martin and O'Kroy 1993; Wagner 2006). As a consequence of arterial desaturation, arterial oxygen content (CaO_2) and O_2 availability for the muscles decrease. In trained subjects, a possible relative hypoventilation (Benoit et al. 1995) or a greater O_2 diffusion limitation in the pulmonary capillaries linked to a high cardiac output (Dempsey et al. 1982; Wagner et al. 1986) could account for this greater arterial O_2 desaturation than in sedentary subjects. However, these hypotheses remain to be validated by conclusive experimental evidence.

Furthermore, in severe acute hypoxia (Calbet et al. 2003) and at altitudes above 4,000 m (Adams and Welch 1980; Fulco et al. 1998), previous studies have shown that the $\dot{V}O_{2max}$ decrement could not be explained only by the reduction in CaO_2. At 5,300 m, two thirds of the $\dot{V}O_{2max}$ decrease is accounted for by CaO_2 reduction and one third by the decrease in peak cardiac output ($\dot{Q}_{max}$) and muscle blood flow (Calbet et al. 2003). Nevertheless, although the decrease in $\dot{Q}_{max}$ is a well accepted fact in severe acute hypoxia, the effect of moderate acute hypoxia on $\dot{Q}_{max}$ is still under debate since it was found decreased (Ekblom et al. 1975; Hopkins et al. 2003; Peltonen et al. 2001) or unchanged (Hartley et al. 1973; Horstman et al. 1980; Hughes et al. 1968; Stenberg et al. 1966; Wagner et al. 1986).

As discussed recently, many studies remain to be performed to solve the controversy between central and peripheral limitation of $\dot{V}O_{2max}$ (Saltin and Calbet 2006; Wagner 2006). di Prampero and Ferretti (1990) support the hypothesis that the limits in $\dot{V}O_{2max}$ are multifactorial and identify the O_2 path from the environment to the mitochondria as a cascade of resistances in series. In this context, in normoxia, the convective O_2 transport represents the greatest role, ~70%, as a limiting factor of $\dot{V}O_{2max}$, the 30% resting depending on the peripheral factors (di Pamprero and Ferretti 1990). Thus, if maximal O_2 transport is a primary determinant factor of $\dot{V}O_{2max}$ (di Pamprero and Ferretti 1990, Saltin and Calbet 2006), tissue O_2 extraction could also play an important role especially in hypoxia (Roca et al. 1989; Wagner 1993, 2006). A recent theoretical study indicated that under normoxia and moderate hypoxia, limitations in both convective and diffusive O_2 transport to the tissues are important factors of $\dot{V}O_{2max}$ (McGuire and Secomb 2004). Thus, convective and diffusive components may contribute differently to the limitation in $\dot{V}O_{2max}$ and may be affected differently by hypoxia in trained and untrained people.

We hypothesized that (1) at these moderate altitudes, contrarily to severe acute hypoxia, changes in maximal oxygen transport are due to the drop of CaO_2 and not of $\dot{Q}_{max}$ (2) the high level of muscle O_2 extraction in trained subjects play a primary role in the $\dot{V}O_{2max}$ decrement in acute hypoxia and limits the uploading of O_2 at the pulmonary level, (3) the relative hypoventilation in trained subjects contributes to aggravate the $\dot{V}O_{2max}$ decrement in acute hypoxia.

Methods

Subjects

Sixteen healthy non smoking males (aged 18–35 years), sea level residents, were recruited for this study. Subjects were divided into two groups: trained (TS) and untrained subjects (US). The trained participants were triathletes, performing at least five training sessions per week and showing a $\dot{V}O_{2max} > 60\,ml\,min^{-1}\,kg^{-1}$. Untrained subjects were sedentary or active in recreational sports, but had never been engaged in systematic endurance training and had a $\dot{V}O_{2max} < 50\,ml\,min^{-1}\,kg^{-1}$. Characteristics of trained and untrained subjects are presented in Table 1. After being informed of the nature of the experiment, each subject gave his written consent to participate in the study. All procedures were approved by the ethics committee of Necker Hospital, Paris.

Protocol

Each subject completed four maximal cycle ergometer tests (Jaeger ER 800, Wuerzburg, Germany) divided into two experimental testing sessions, each separated by about 7 days and with at least a 3-h rest between tests. The first test was always carried out in normoxia (F_IO_2 = 0.209 and P_IO_2 = 150 mmHg). In the other tests, subjects breathed inspired oxygen fractions of 0.187, 0.154 and 0.117 (P_IO_2 of 132, 108 and 81.5 mmHg, respectively) at the normobaric pressure (~760 mmHg) for simulated altitudes of approximately 1,000, 2,500 and 4,500 m, respectively. Subjects were blinded to the altitude used for each test, and the session order was randomized. To simulate theses altitudes we used the AltiTrainer$_{200}$® (S.M.TEC, Geneva, Switzerland) which produces a normobaric hypoxic mixture (reduced oxygen fraction) by addition of

Table 1 Characteristics of trained (n = 8) and untrained (n = 8) subjects

	US	TS
Age (years)	25.0 ± 1.5	28.6 ± 1.0
Body mass (kg)	69.9 ± 2.5	71.5 ± 2.9
Height (m)	1.75 ± 0.20	1.78 ± 0.31

Values are mean ± SE

US untrained subjects, *TS* trained subjects

nitrogen in ambient air. Before starting exercise, subjects remained at rest breathing the desired gas mixture during 5 min for physiological parameters to stabilize. The exercise began with a 3-min warm-up at a power output (PO) of 60 W followed by an incremental load of 30 W every 2 min, until the subjects could no longer maintain a pedaling frequency of 70 rev min^{-1}. Subjects were verbally encouraged to continue exercise as long as possible. The test was considered to be maximal if two of the following three criteria were met: (1) a plateau in $\dot{V}O_2$ ($\leq$ 150 ml increase over 2 min) despite increasing power output, (2) a respiratory exchange ratio >1.1 at exhaustion, (3) Lactate concentration at maximal exercise >9 mmol l^{-1}.

Gas exchange

Gas exchange was recorded breath by breath at rest, during exercise and during recovery. We used a rigid mouthpiece connected to a ''Y'' system fixation with a double valve which ensures separate ways between inspired and expired flow (Jaeger, Wuerzburg, Germany). An inspiratory valve, connected to the $AltiTrainer_{200}$® allowed the subject to inhale the hypoxic mixture. Expired gases were collected continuously into a metabograph (Oxycon, Jaeger, Wuerzburg, Germany) to measure expired minute ventilation at body temperature and pressure saturated and expressed at the prevailing normobaric pressure ($\dot{V}E_{BTPS}$), O_2 consumption ($\dot{V}O_2$), end-tidal carbon dioxide pressure ($PetCO_2$) and tidal volume (VT). Alveolar O_2 pressure (PAO_2) was calculated using the Riley alveolar gas equation (Riley et al. 1946):

$PAO_2 = P_IO_2 - PACO_2/R$. Where R *is* $\dot{V}CO_2/\dot{V}O_2$ and $PACO_2 = PetCO_2$.

Ventilatory equivalents ($\dot{V}E/\dot{V}O_{2max}$ and $\dot{V}E/\dot{V}CO_{2max}$) were calculated at maximal exercise. The PO_2 alveolo-arterial difference (mmHg) was calculated as: $A\text{-}a'DO_2 = PAO_2 - Pa'O_2$.

Blood analyses

Capillary blood from a prewarmed earlobe with a vasodilating capsaicin cream was sampled at rest and at maximal exercise to measure arterialized PO_2 ($Pa'O_2$), $PaCO_2$ ($Pa'CO_2$), O_2 saturation ($Sa'O_2$), pH (pHa'), hemoglobin concentration ([Hb]), lactate and bicarbonate concentrations [Radiometer ABL 700, Copenhagen, Denmark]. The earlobe was always physically rubbed with a compress in order to activate blood circulation and ameliorate the cream penetration. Then, we applied a warming cream for at least 10 to 20 min (capsaïcin cream: Disalgyl* Monin). The accuracy of arterialized capillary blood sampling compared to arterial sampling being very much operator-dependent, a technician was especially trained in our laboratory to perform the arterialized measurements that have already been used and compared with arterial values in pathological conditions (Lamberto et al. 2004). To avoid air contamination, when the capillary sampling procedure lasted more than 15 seconds, the sample was discarded and the sampling repeated.

Heart rate (HR) was measured continuously using electrocardiography. Cardiac output ($\dot{Q}$) was measured using a non invasive impedance cardiograph device, the PhysioFlow PF-05 (Manatec biomedical, Paris, France). The PhysioFlow concept and methodology have been recently validated at rest and at exercise (Charloux et al. 2000) and during a maximal progressive exercise (Richard et al. 2001; Welsman et al. 2005). This bioimpedance method of $\dot{Q}$ determination uses changes in thoracic impedance during cardiac ejection to calculate stroke volume (SV). Six electrodes were placed, two for the electrocardiogram and four ''impedance'' electrodes placed at the base of the neck and on the processus xiphoideus. Before placing these electrodes, the skin was slightly scraped with an abrasive sponge and cleaned with alcohol. After placing the electrodes the thread was carefully fixed with an adhesive band in order to prevent any movement. The subject takes its sitting position on the ergocycle and keeps quiet and silent during all the calibration process. The measurement of arterial pressure was necessary to start the calibration process. We took the arterial pressure three times (after 5 min in hypoxic conditions) and kept the last value. We watched over the signal quality and stability during the entire test. $\dot{Q}$ was continuously measured during the test and averaged over 15-s intervals. The calibration procedure was performed at rest before each exercise test, the subject being in normoxic or hypoxic conditions.

Parameters of convective O_2 transport to the tissue were calculated at maximal exercise

Arterialized O_2 content ($ml\,l^{-1}$) : $Ca'O_{2max} = [Hb]^* 13.4^* Sa'O_{2max}/100 + Pa'O_{2max}{}^*0.003$. With [Hb] in g dl^{-1}, $Sa'O_{2max}$ in % and $Pa'O_{2max}$ in mmHg.

Maximal O_2 transport ($l\,min^{-1}$) : $\dot{Q}aO_{2max} = \dot{Q}_{max}{}^*Ca'O_{2max}/1,000$.

Parameters of diffusive O_2 transport to the tissue were calculated at maximal exercise

Difference in arterial-venous O_2 content ($ml\,l^{-1}$) : $Da\text{-}\bar{v}O_{2max} = (\dot{V}O_{2max}/\dot{Q}_{max})^* 1,000$ with $\dot{V}O_{2max}$ and $\dot{Q}_{max}$ in $l\,min^{-1}$.

Mixed venous O_2 content (ml l^{-1}) : $C\bar{v}O_{2max} = Ca'O_{2max} - Da\text{-}\bar{v}O_{2max}$.
Mixed venous O_2 saturation (%): $S\bar{v}O_{2max} = (C\bar{v}O_{2max}{}^{*}100)/([Hb]^{*}13.4)$ neglecting dissolved venous O_2 content.
Tissue O_2 extraction (%): $O_2ER_{max} = \dot{V}O_{2max}/\dot{Q}aO_{2max}$.

We used Dill and Forbes blood O_2 line charts to convert $S\bar{v}O_{2max}$ to $P\bar{v}O_{2max}$ in reference with pH and with a theoretical body temperature of 38.5°C at maximal exercise (Altman 1961).

An estimation of the hypoxic ventilatory response at exercise (HVRe) in US and TS has been calculated from our measurements, in reference with the hypoxic ventilatory response test at exercise developed by Richalet et al. (1988). HVRe was calculated as the ratio of the difference in minute ventilation $(\Delta\dot{V}E)$ and arterial saturation $(\Delta\ SaO_2)$ between normoxia and 4,500 m at an absolute workload equivalent to 30% of normoxic $\dot{V}O_{2max}$. $HVRe = (\Delta\dot{V}E/\Delta SaO_2)/\text{body weight} \times 100$.

Statistical analysis

A two-way analysis of variance (ANOVA) for repeated measures was used to analyze the effect of altitude on measured parameters and the differences between the two groups. If a main effect of hypoxia appeared a Scheffe post-hoc test was used to identify the altitude at which there was a significant difference from normoxia for each group. Relationships between two different parameters were examined by linear regressions. Values are given as mean ± standard error (SE) and the level of significance was established at $P < 0.05$.

Results

Aerobic performance

$\dot{V}O_{2max}$ was greater in TS than in US in normoxia and at each altitude. The decrement in $\dot{V}O_{2max}(\Delta\dot{V}O_{2max})$ was significant at and above 1,000 m in both groups (Table 2). In absolute values, the decrease in $\dot{V}O_{2max}$ was significantly greater in TS at and above 1,000 m. $\Delta\dot{V}O_{2max}$ in relative values was greater in TS than in US at 4,500 m (Table 2).

Ventilatory parameters and pulmonary gas exchange

$\dot{V}E_{max}$, expressed at the prevailing normobaric pressure, was not significantly affected by training status but there was a decrement in $\dot{V}E_{max}$ in TS at 4,500 m in comparison with sea level (Table 3). $\dot{V}E/\dot{V}O_2$ at maximal exercise was significantly lower in TS than in US at each altitude and higher at 4,500 m compared to normoxia for TS and US (Table 3). $\dot{V}E/\dot{V}CO_{2max}$ increased at 4,500 m in both groups and was significantly lower in TS at this altitude in comparison with US. VT remained unchanged. PAO_{2max} decreased from 1,000 m in trained and untrained subjects but without difference between groups (Table 3). $PetCO_2$ was higher in TS at all altitudes but the difference with US was significant only at sea level (Table 3). The estimated hypoxic ventilatory response at exercise was lower in TS (0.48 ± 0.20 $\text{l min}^{-1}\ \text{kg}^{-1}$) than in US (0.79 ± 0.38 $\text{l min}^{-1}\ \text{kg}^{-1}$, $P < 0.05$). When values were pooled, there was a correlation between $\dot{V}E_{max}(\text{l min}^{-1})$ and $\dot{V}O_{2max}(\text{ml min}^{-1}\ \text{kg}^{-1})$: $\dot{V}O_{2max} = 13.83 + 0.25\ \dot{V}E_{max}$, $R = 0.51$, $P < 0.05$. A-a′DO_{2max} was greater in TS than in US at each altitude and significantly lower at 4,500 m compared to sea level in TS (Table 3).

Parameters of convective O_2 transport to the tissues

Results are presented in Table 4 and Fig. 1 and 2. At every altitude, HR_{max}, Sa′O_{2max} were significantly lower and SV_{max}, $\dot{Q}_{max}$ greater in TS than in US (Figs. 1, 2). There was no difference in pHa' and [Hb] between TS and US, but in both groups pHa' increased at 4,500 m (Table 4). SV_{max} and $\dot{Q}_{max}$ were not affected by hypoxia in both groups. Furthermore, there was a tendency to a decrease in $\dot{Q}_{max}$ at 4,500 m in TS, but without significant difference from normoxia. The decrease in Sa′O_{2max} was

Table 2 Aerobic performance parameters

	Sea level		1,000 m		2,500 m		4,500 m	
	US	TS	US	TS	US	TS	US	TS
$\dot{V}O_{2max}(\text{ml min}^{-1}\ \text{kg}^{-1})$	43.3 ± 2.1	65.5** ± 1.8	42* ± 2.2	62.7*,** ± 1.9	39.4* ± 2.2	57.7*,** ± 1.8	35.7* ± 1.8	46.4*,** ± 1.8
$\Delta\dot{V}O_{2max}(\text{ml min}^{-1}\ \text{kg}^{-1})$			–1.4* ± 0.3	–2.8*,** ± 0.4	–3.9* ± 0.3	–7.8*,** ± 0.7	–7.6* ± 0.6	–19*,** ± 1.4
$\Delta\dot{V}O_{2max}(\%)$			–3.2* ± 0.8	–4.31* ± 0.6	–9.1* ± 1.0	–11.9* ± 1.0	–17.6* ± 1.1	–29.1*,** ± 1.9

Values are mean ± SE

US untrained subjects, *TS* trained subjects, $\dot{V}O_{2max}$, maximal O_2 consumption

*Significantly different from sea level ($P < 0.05$). $n = 8$ in each group; **Significantly different from untrained group ($P < 0.05$)

Table 3 Pulmonary ventilation and gas exchanges parameters at maximal exercise

	Sea level		1,000 m		2,500 m		4,500 m	
	US	TS	US	TS	US	TS	US	TS
$\dot{V}E$(l min^{-1} BTPS)	133.2 ± 9.5	156.1 ± 6.4	126.8 ± 8.3	146.3 ± 4.6	127.5 ± 9.6	145.3 ± 4.8	130 ± 9.9	133 ± 7.5*
$\dot{V}E/\dot{V}O_2$	44.3 ± 2.6	33.9** ± 2.1	43.7 ± 2.4	33.1** ± 1.6	49 ± 2.5	35.6** ± 1.5	55.3* ± 4.4	40.5*,**± 2.7
$\dot{V}E/\dot{V}CO_2$	36.8 ± 2.2	31.7 ± 2.7	36.4 ± 1.7	34.2 ± 3.9	39.7 ± 2.1	40.2 ± 4.1	46.2* ± 1.9	39.7*,** ± 3.2
PAO_2 (mmHg)	124.1 ± 1.3	120.1 ± 1.9	103.1* ± 1.4	105.4* ± 2.5	84.2* ± 1.1	84.7* ± 2.2	61.6* ± 1.7	58.4* ± 1.8
$PetCO_2$ (mmHg)	31.9 ± 1.4	36.4** ± 0.9	32.6 ± 1.6	36.8 ± 1.9	29.1* ± 1.6	30.9 ± 1.9	25.7* ± 1.1	28.3* ± 1.8
VT (l)	2.95 ± 0.09	3.22 ± 0.14	2.98 ± 0.11	3.21 ± 0.17	29.1 ± 1.6	2.93 ± 0.11	3.04 ± 0.1	3.17 ± 0.18
A-a'DO2 (mmHg)	24.6 ± 2.3	35.1** ± 2.3	24.2 ± 2.9	37.2** ± 2.2	25.1 ± 2.6	34.6** ± 2.6	22.2 ± 1.4	25.4*,** ± 1.1

Values are mean ± SE

US untrained subjects, *TS* trained subjects, *VT* Tidal volume $\dot{V}E$, expired ventilation expressed at the prevailing normobaric pressure; $\dot{V}E/\dot{V}O_2$, ventilatory equivalent; PAO_2, alveolar O_2 pressure; $PetCO_2$, end-tidal carbon dioxide pressure; $A\text{-}a'DO_2$, alveolar-arterialized PO_2 difference

*Significantly different from sea level ($P < 0.05$). $n = 8$ in each group; **Significantly different from untrained group ($P < 0.05$)

Table 4 Cardiovascular and blood gas parameters at $\dot{V}O_{2max}$

	Sea level		1,000 m		2,500 m		4,500 m	
	US	TS	US	TS	US	TS	US	TS
Δ HR (beat min^{-1})			–5.3* ± 0.7	–3** ± 0.6	–6.9* ± 1.6	–4.5* ± 1.4	–9* ± 1.5	–12.5* ± 1.6
Δ HR (%)			–2.7* ± 0.34	–1.7 ± 0.38	–3.5* ± 0.84	–2.4* ± 0.74	–4.7* ± 0.77	–7* ± 0.91
[Hb] (g dl^{-1})	17.1 ± 0.32	16.3 ± 0.27	16.7 ± 0.27	16.3 ± 0.28	16.8 ± 0.25	16.0 ± 0.29	16.9 ± 0.28	16.1 ± 0.23
$Pa'O_2$ (mmHg)	99.5 ± 1.7	82.6** ± 3.7	79.3* ± 2.2	66.5*,** ± 1.6	58.8* ± 2.1	49.4*,** ± 1.6	39.3* ± 1.1	34.1*,** ± 1.1
$Pa'CO_2$ (mmHg)	31.3 ± 1.9	33.7 ± 1.5	29.9 ± 1.6	33.9 ± 1.5	30.2 ± 1.8	32.1 ± 1.3	27.7 ± 0.5	28.6* ± 0.5
$C\bar{v}O_2$(mlO_2 l^{-1})	87.2 ± 5.4	33.5** ± 5.7	78.1* ± 7.4	29.9** ± 5.0	72.5* ± 6.4	22.3*,** ± 4.9	48.2* ± 7.6	13.5*,** ± 3.4
$P\bar{v}O_2$ (mmHg)	24.9 ± 1.1	12.9** ± 1.8	23.4 ± 1.6	11.1** ± 1.8	20.6* ± 1.2	8.6*,** ± 1.7	14.9* ± 1.6	5.9*,** ± 1.4
pHa'	7.30 ± 0.14	7.27 ± 0.14	7.30 ± 0.13	7.32 ± 0.10	7.32 ± 0.12	7.31 ± 0.23	7.36* ± 0.12	7.34* ± 0.13
Lactate	12.9 ± 1.15	13.2 ± 1.1	13.2 ± 0.9	10.6 ± 0.7	11.3 ± 0.8	11.1 ± 1.3	12.7 ± 0.4	12.1 ± 1.3

Values are mean ± SE

US untrained subjects, *TS* trained subjects, *HR* heart rate, *[Hb]* hemoglobin concentration; $Pa'O_2$, arterialized PO_2; $Pa'CO_2$, arterialized PCO_2; pHa', arterialized pH; $C\bar{v}O_2$ venous oxygen content, $P\bar{v}O_2$ venous PO_2

**Significantly different from untrained group ($P < 0.05$); *Significantly different from sea level ($P < 0.05$). $n = 8$ in each group

significant at and above 1,000 m for TS and 2,500 m for US (Fig. 2). ΔHR_{max} was significant from 1,000 m in US and only from 2,500 m in TS (Table 4). $Ca'O_{2max}$ was greater in US than in TS at each level of hypoxia and decreased at and above 1,000 m for TS and US (Fig. 2). $\dot{Q}aO_{2max}$ was greater in TS than in US except at 4,500 m (Fig. 2). When pooling all the altitudes, there was a correlation between $\Delta\dot{V}O_{2max}$ and $\dot{Q}aO_{2max}$ decrement ($\Delta\dot{Q}aO_{2max}$) in hypoxia ($P < 0.05$, $R = 0.92$ in US and $R = 0.96$ in TS).

Parameters of tissue O_2 extraction

Da-$\bar{v}O_{2max}$ was greater in TS than in US except at 4,500 m (Fig. 3). The decrease in Da-$\bar{v}O_{2max}$ and $P\bar{v}O_{2max}$ was significant at and above 2,500 m for TS and US. $S\bar{v}O_{2max}$ (Fig. 3) and $C\bar{v}O_{2max}$ were lower in TS at all altitudes and decreased significantly at and above 1,000 m in US and 2,500 m in TS (Table 4). Trained subjects had a greater tissue O_2 extraction (O_2ER_{max}) than untrained ones in normoxia and at all levels of hypoxia. O_2ER_{max} increased with hypoxia in both groups at 4,500 m (Fig. 3) but the relative increase in O_2ER_{max} was smaller in TS than US. When pooling all the altitudes, there was a correlation between $\Delta\dot{V}O_{2max}$ and Da-$\bar{v}O_{2max}$ decrement (ΔDa-$\bar{v}O_{2max}$) in acute hypoxia ($P < 0.05$, $R = 0.89$ in US and $R = 0.97$ in TS).

Discussion

Critique of methods

For ethical reasons, this study used two non invasive methods. The first one concerns the use of arterialized

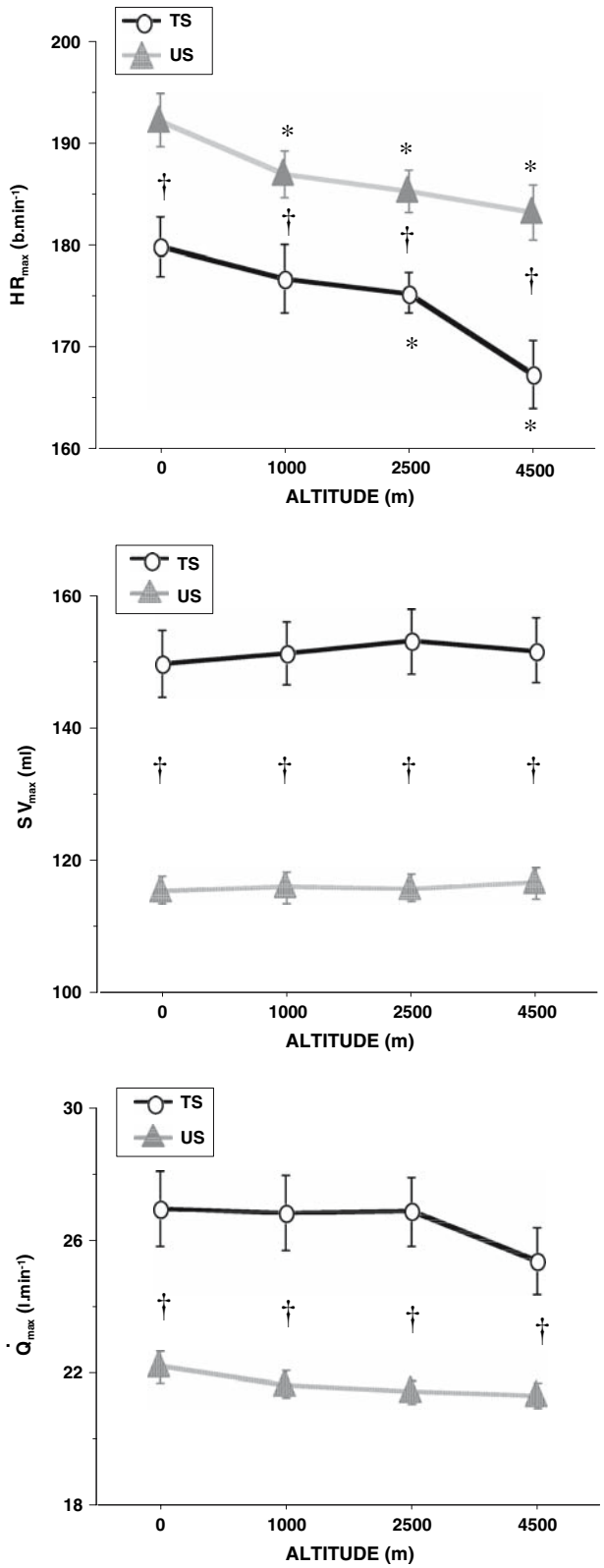

Fig. 1 Maximal heart rate (HR_{max}), maximal stroke volume (SV_{max}) and maximal cardiac output ($\dot{Q}_{max}$) in acute hypoxia. Values are mean ± SE. TS, trained subjects; US, untrained subjects. *Significantly different from normoxia ($P < 0.05$). †Significantly different from untrained group ($P < 0.05$)

capillary blood rather than arterial blood samples. The second concerns cardiac output measurement with the impedancemetry technology. Although they were previously validated, there is no consensus about the reliability of these two methods. Nevertheless, we were very rigorous in the use of these two methodologies. In the literature, the relationship between $\dot{V}O_{2max}$ and cardiac output shows that 5.9–7.5 l min^{-1} of cardiac output is needed per liter of $\dot{V}O_{2max}$ (Saltin and Calbet 2006). Our values of cardiac output are in agreement with these results. Concerning PaO_2, it was shown that arterialized earlobe PO_2 at exercise was slightly lower than arterial PO_2 in most cases and also that the differences decreased as arterial PO_2 decreased (Fajac et al. 1998). This result suggests that our arterialized PO_2 values could be slightly lower than arterial values especially in normoxia, whereas in hypoxia the difference would be minimal. Errors in measured PO_2 will clearly affect the exactitude of calculated variables. Nevertheless these errors decrease with the severity of hypoxia especially at 4,500 m, which is the most important altitude of interest of this paper, and cannot significantly interfere in the difference between trained and untrained subjects. Furthermore, considering that exercise duration and/or intensity was not equal for all subjects, we cannot exclude the fact that blood temperature at exercise was variable among subjects and could slightly influence the values of $Pa'O_2$.

Even with these caveats, we are convinced that the data reported above are basically correct. They will be discussed in the sections that follow.

In normoxia, as expected, in spite of a lower HR_{max}, TS have a greater $\dot{Q}_{max}$ because of a greater SV_{max} than US. This important $\dot{Q}_{max}$ allowed TS to have a greater $\dot{Q}aO_{2max}$, in spite of a lower $Ca'O_{2max}$ mainly due to a lower $Sa'O_{2max}$. Furthermore, as shown with their lower $S\bar{v}O_{2max}$, TS have a greater O_2ER_{max} than US.

In hypoxia, this study indicates a significant decrease in aerobic performance at and above 1,000 m for the two populations. Maximal lactate concentrations are similar in all conditions, suggesting that subjects actually performed at their maximum. The comparison between trained and untrained subjects shows a larger decrease in $\dot{V}O_{2max}$ in TS than US at 4,500 m.

Several parameters could account for the greater decrease in aerobic performance in TS than US in moderate acute hypoxia.

Ventilatory parameters

Our results confirm a positive correlation between maximal ventilation and $\dot{V}O_{2max}$. Therefore, subjects who have the greater $\dot{V}O_{2max}$ have the greater maximal ventilation. $\dot{V}E_{max}$ was lower in TS at 4,500 m in comparison with sea

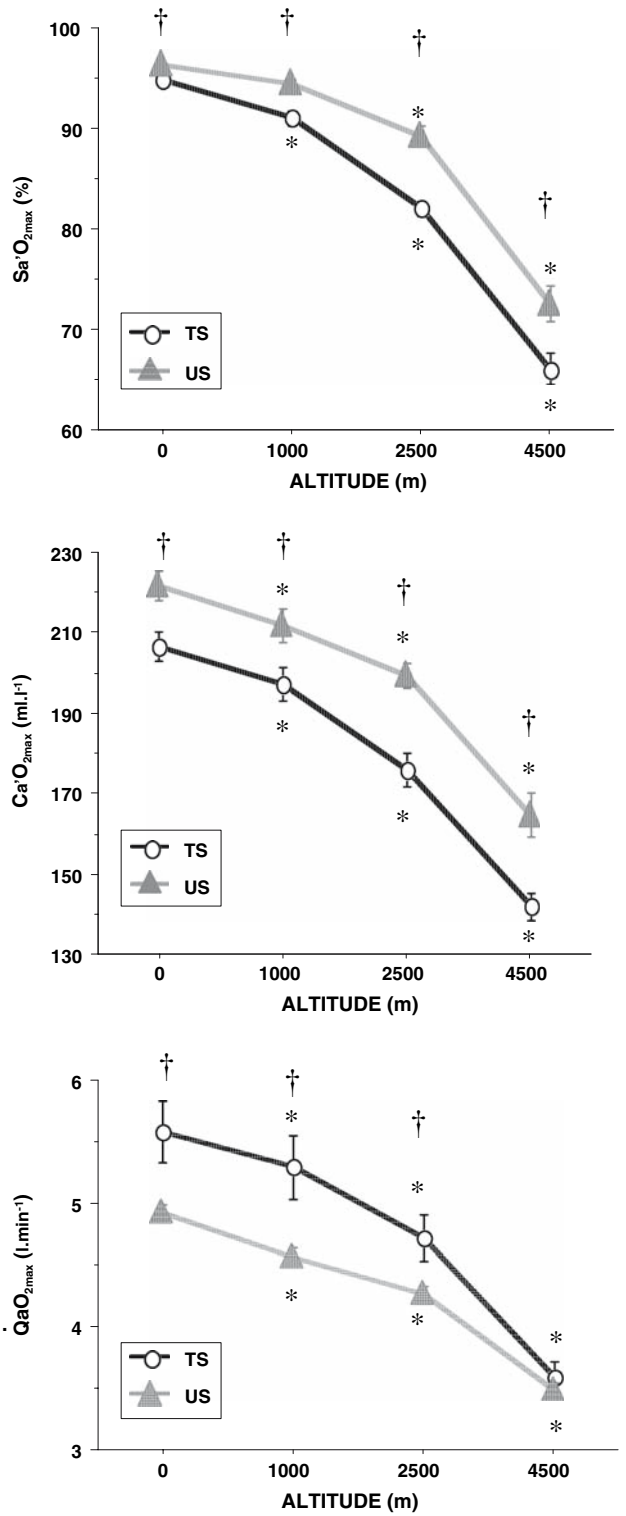

Fig. 2 Arterialized O_2 saturation ($Sa'O_{2max}$) and content ($Ca'O_{2max}$) at maximal exercise and maximal O_2 transport ($\dot{Q}aO_{2max}$). Values are mean ± SE. *TS* trained subjects, *US* untrained subjects. *Significantly different from normoxia ($P < 0.05$). †Significantly different from untrained group ($P < 0.05$)

level. Thus, $\dot{V}E_{max}$ is more affected by hypoxia in TS. This difference in $\dot{V}E_{max}$ between TS and US has a consequence on $\dot{V}E/\dot{V}O_{2max}$. Indeed with regard to $\dot{V}E/\dot{V}O_{2max}$ (Table 3), our results confirm the relative hypoventilation in TS as shown by the lower HVRe in TS. However, differences between US and TS in PAO_2 and $PetCO_2$ do not reach significance at altitude. Moreover, in US, $\dot{V}E/\dot{V}O_{2max}$ increases with altitude because of $\dot{V}O_{2max}$ decrement, whereas $\dot{V}E_{max}$ remained unchanged. In TS, $\dot{V}O_{2max}$ decrement was greater than in US, however $\dot{V}E_{max}$ also decreased. In consequence, in TS, $\dot{V}E/\dot{V}O_{2max}$ also increased with hypoxia, but with a tendency to be lower than in US ($\Delta\dot{V}E/\dot{V}O_{2max} = 6.9 \pm 2.4$ vs 11.3 ± 3.1, TS vs US, 4,500 m, p=0.07). Thus, in acute hypoxia the relative hypoventilation in TS is accentuated in comparison with normoxia. We could estimate that if TS were able to keep the normoxic $\dot{V}E_{max}$ value at 4,500 m, i.e by 23 l min^{-1}, it would impact PAO_2 by 4.9 mmHg and thus $Sa'O_{2max}$ decrement by around 4%. Thus, in TS, the more important $\dot{V}E_{max}$ sensitivity to acute hypoxia and the relative hypoventilation could contribute by 50% to a lower $Sa'O_{2max}$ and thus a greater $\dot{V}O_{2max}$ decrement at 4,500 m in this group.

O_2 transport

Maximal O_2 transport is the product of maximal cardiac output and arterial O_2 content. $\dot{Q}_{max}$ remained unchanged in moderate acute hypoxia. This result is in agreement with previous studies (Hartley et al. 1973; Horstman et al. 1980; Hughes et al. 1968; Stenberg et al. 1966; Wagner et al. 1986). However, this is the first study to show a similar trend in trained and untrained subjects. In moderate acute hypoxia, the decrease in HR_{max} is now a well accepted fact and there are many hypotheses about this decrement. However, the precise mechanisms of this HR_{max} decline remain to be identified. On the other hand, $Ca'O_{2max}$ decreased in TS and US at and above 1,000 m. This greater decrement in TS is fully explained by the difference in $Sa'O_{2max}$ since [Hb] changes are similar in both groups. Finally, the $\dot{Q}aO_{2max}$ decrement, significant at and above 1,000 m in both groups, is fully explained by the drop in $Sa'O_{2max}$. At 4,500 m in TS, the greater arterial O_2 desaturation explains that there is no more difference in $\dot{Q}aO_{2max}$ between groups. The position of the oxyhemoglobin dissociation curve could also affect O_2 saturation. However, there is no difference between groups in pH at maximal exercise (Table 4). Thus, this parameter could not explain the difference in $Sa'O_{2max}$ between trained and untrained subjects.

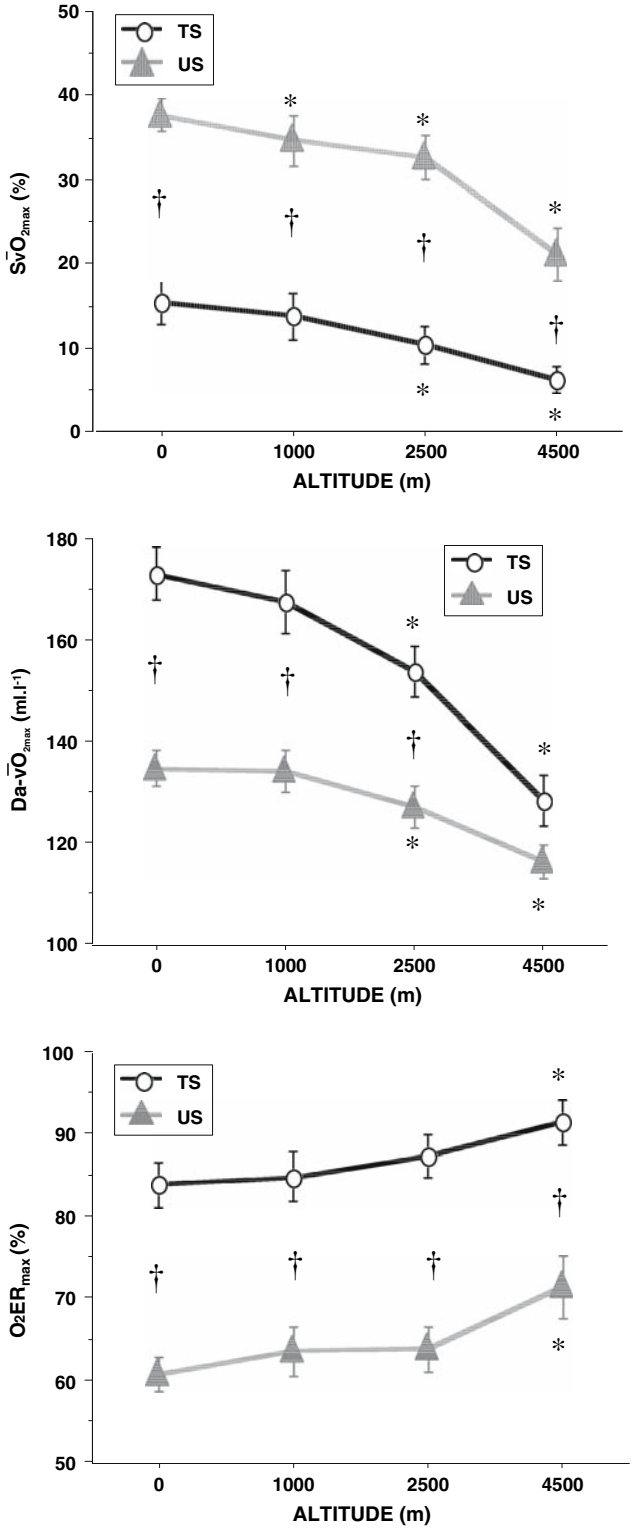

Fig. 3 Mixed venous O_2 saturation ($S\bar{v}O_{2max}$), arterio-venous O_2 difference (Da-$\bar{v}O_{2max}$) and tissue O_2 extraction (O_2ER_{max}). Values are mean ± SE. *TS* trained subjects, *US* untrained subjects. *Significantly different from normoxia ($P < 0.05$). †Significantly different from untrained group ($P < 0.05$)

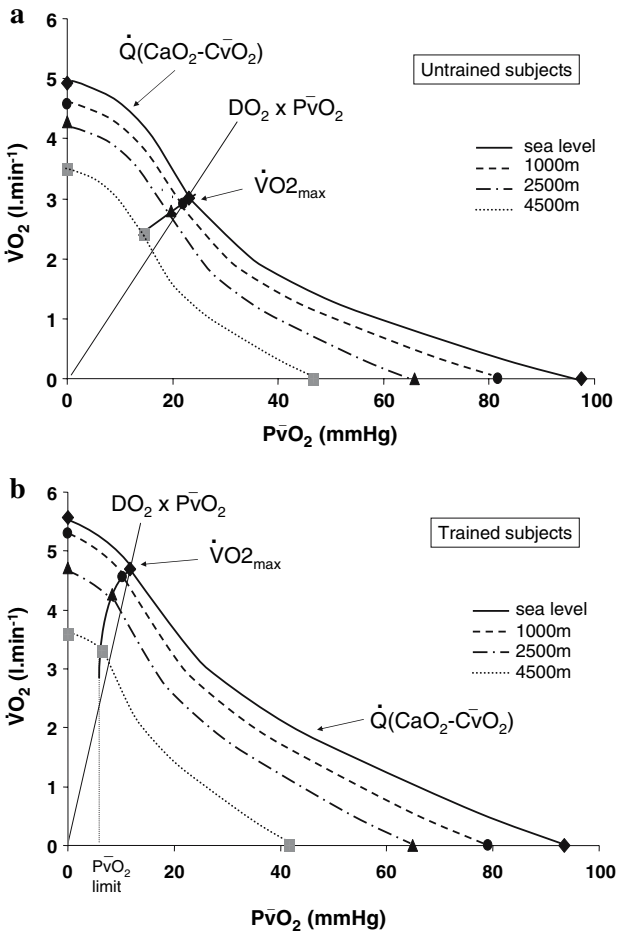

Fig. 4 In reference with previous studies from Wagner and others (Hogan et al. 1988; 1989; Wagner 1988),$\dot{V}O_{2max}$ can be represented as the point of intersection of two curves (1) *a curve of negative slope* showing oxygen uptake calculated from Fick principle: $\dot{Q}(CaO_2 - C\bar{v}O_2)$ (2) *a curve of positive slope* through the origin reflecting Fick's law of diffusion: $DO_2 \times P\bar{v}O_2$. The Fick curve is curvilinear because of the nonlinearity of the O_2 dissociation curve. Figure 4a concerns untrained subjects and Figure 4b trained subjects

There is a correlation between $\Delta\dot{V}O_{2max}$ in hypoxia and $\Delta\dot{Q}aO_{2max}$ in both populations. The more important $\dot{Q}aO_{2max}$ decrement in TS in comparison with US could partly explain the greater $\dot{V}O_{2max}$ decrement in TS at 4,500 m. As mentioned before, at this altitude, there is no more difference in $\dot{Q}aO_{2max}$ between TS and US.

Tissue O_2 extraction

Tissue O_2 extraction in normoxia is much greater in TS than in US. Furthermore, in hypoxia the increase in O_2ER_{max} is less important in TS than US (8 vs. 15% at 4,500 m, $P < 0.05$). These results suggest that there is a compensation of the $Sa'O_{2max}$ decline with altitude by an

increase in O_2ER_{max} that would limit the decrease in O_2 availability for the muscle. Indeed, this compensation appears different for the two populations. US could easily increase O_2ER_{max} until 4,500 m, thus limiting the $\dot{V}O_{2max}$ decrement. This compensation is more difficult in TS probably because they approach, even in normoxia, the physiological upper limit of O_2ER_{max} as witnessed by the very low value of $S\bar{v}O_{2max}$. This result is confirmed by the dramatic decrease in Da-$\bar{v}O_{2max}$ in TS at 4,500 m. At this altitude, there is no more difference between groups. At 4,500 m $P\bar{v}O_{2max}$ is about 6 mmHg in TS indicating that the muscle venous PO_2 is probably close to zero. At ~ 4,500 m, a previous study reported values of $P\bar{v}O_{2max}$ about 13 mmHg (Wagner et al. 1986). These values are slightly higher than our calculated $P\bar{v}O_{2max}$ in TS but similar than our values in US. However, a study indicated that subjects with a highest $\dot{V}O_{2max}$ (after training) showed a lowest $P\bar{v}O_{2max}$ (Roca et al. 1992), suggesting a crucial dependence of $P\bar{v}O_{2max}$ in training status. In our study, focused on highly endurance trained subjects, the low $P\bar{v}O_{2max}$ values are therefore in accordance with this hypothesis. In TS at 4,500 m, $S\bar{v}O_{2max}$ could no more decrease and therefore could not compensate the decrease in SaO_{2max}. This result is presented in Fig. 4, where we can see in US a linear decrement in $\dot{V}O_{2max}$ with decreasing $P\bar{v}O_2$. This is not true in TS because at 4,500 m $P\bar{v}O_{2max}$ probably reaches its lower limit. Increasing tissue O_2 extraction by increasing muscle capillaries is a potent physiological adaptation to training at sea level. However, this adaptation in hypoxia becomes a disadvantage (especially at 4,500 m) because TS can no more increase O_2ER_{max} to compensate the SaO_{2max} decrement. Therefore, tissue O_2 extraction could also partly explain the difference in $\dot{V}O_{2max}$ decrement between trained and untrained subjects at 4,500 m.

The role of pulmonary diffusion limitation

At maximal exercise the alveolar-arterial O_2 difference is significantly greater in TS than US at each altitude and lower at 4,500 m than at sea level in TS (Table 3). Thus A-a′DO_{2max} is not aggravated by hypoxia but reduced in TS at 4,500 m. Previous studies showed an alteration in pulmonary gas exchange in hypoxia linked to an increase in ventilation-perfusion inequality $(\dot{V}A/\dot{Q}c)$ and alveolar-pulmonary capillary diffusion limitation (Torre-Bueno et al. 1985; Wagner et al. 1986). Furthermore, to explain the decrease in $A\text{-}a'DO_{2max}$ in TS at 4,500 m the increase in pulmonary arterial pressure could enhance the capillary recruitment, increasing the surface area for gas exchange (Hillier et al. 1997). However, this hypothesis remains to be validated. We have seen that an increase of O_2ER_{max} could limit the drop of O_2 availability for the muscle. However, this compensation is not favorable for pulmonary gas exchange. The diffusion limitation across the alveolar-arterial interface, resulting from increased cardiac output and reduced blood transit time (TT) in the pulmonary capillary could impair the alveolar-capillary O_2 exchange (Dempsey et al. 1982; Wagner et al. 1986). In normoxia, diffusion limitation appears in elite athletes with a high $\dot{V}O_2(>4-51\,min^{-1})$. In the present study, the non significant decrease in $\dot{Q}_{max}$ in moderate acute hypoxia suggests that in hypoxic conditions, the erythrocyte transit time in pulmonary capillaries is not modified and probably does not contribute per se to the hypoxia-induced decrease in $Sa'O_{2max}$. Another factor could contribute to aggravate the diffusion limitation in moderate hypoxia. The lower $S\bar{v}O_2$ at maximal exercise could have two opposite consequences on $A\text{-}a'DO_2$. It increases the amount of O_2 necessary to diffuse in order to reach a given SaO_2. In another hand, it increases the alveolar-capillary PO_2 gradient, and thus facilitates the O_2 diffusion process. A previous study has shown that at any given PAO_2, $P\bar{v}O_2$ has a considerable influence on the rate of diffusion of O_2 (Wagner 1982). Therefore, situations in which $P\bar{v}O_2$ is low are associated with an increased vulnerability of O_2 exchange to diffusion limitation (Wagner 1982). Thus, the greater arterial desaturation in TS in moderate acute hypoxia, is certainly due to a lower muscle $S\bar{v}O_{2max}$ (because of a greater O_2 extraction), associated with an unchanged $\dot{Q}_{max}$ with altitude. The greater decrease in $Sa'O_{2max}$ than $S\bar{v}O_{2max}$ with altitude explains the dramatic decrease in Da-$\bar{v}O_2$ at maximal exercise. At 4,500 m in TS, $S\bar{v}O_{2max}$ is probably close to its lower limit and can no more compensate $Sa'O_{2max}$ decrement and contributes to aggravate arterial desaturation. Therefore, as $\dot{Q}_{max}$ does not compensate this decrease, $\dot{V}O_{2max}$ is greatly affected, especially in TS.

In conclusion, three of the sequential steps of O_2 transfer from the atmosphere to the tissues present differences between trained and untrained subjects in moderate acute hypoxia (Fig. 5). In trained subjects at 4,500 m, a decrease in maximal ventilation and a greater decrease in maximal O_2 transport than in untrained subjects associated to a lower capacity to increase tissue O_2 extraction could explain the greater $\dot{V}O_{2max}$ decrement in this group. Furthermore, at 4,500 m, the important O_2ER_{max} in trained subjects reaches its limit and contributes to aggravate the decrement in $Sa'O_2$ via the pulmonary diffusion limitation because of an extremely low $P\bar{v}O_2$.

The two main physiological characteristics developed by aerobic training, i.e. increase in heart pumping capacity and increase in muscle ability to extract O_2 have reached their limits in moderate acute hypoxia.

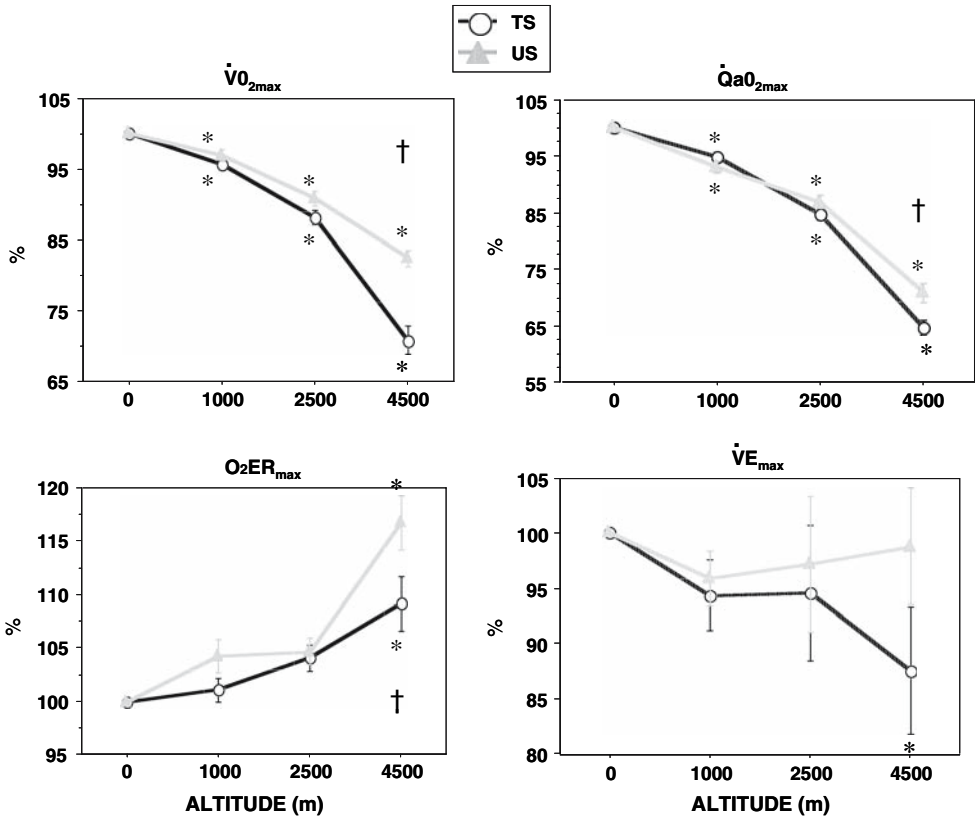

Fig. 5 Changes in $\dot{V}O_{2max}$, $\dot{V}E_{max}$, $\dot{Q}aO_{2max}$ and O_2ER_{max} at each altitude expressed in % from sea level (100% = sea level). Values are mean ± SE. *TS* trained subjects, *US* untrained subjects. *Significantly different from normoxia ($P < 0.05$). † Significantly different from untrained group ($P < 0.05$)

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References

Adams RP, Welch HG (1980) Oxygen uptake, acid–base status, and performance with varied inspired oxygen fractions. J Appl Physiol 49:863–868

Altman PL (1961) Blood O_2 dissociation line charts. In: Dittmer DS (ed) Biological handbook. Blood and other body fluids. Federation of American societies for experimental biology, chap 7, p 165

Benoit H, Busso T, Castells J, Devis C, Geyssant A (1995) Influence of hypoxic ventilatory response on arterial O_2 saturation during maximal exercise in acute hypoxia. Eur J Appl Physiol 72:101–105

Calbet JAL, Boushel R, Radegran G, Sodergaard H, Wagner PD, Saltin B (2003) Determinant of maximal oxygen uptake in severe acute hypoxia. Am J Appl Physiol Regul Integr Comp Physiol 284:R291–R303

Chapman RF, Emery M, Stager JM (1999) Degree of arterial desaturation in normoxia influences $\dot{V}O_{2max}$ decline in mild hypoxia. Med Sci Sports Exerc 31:658–663

Charloux A, Lonsdorfer-Wolf E, Richard R, Lampert E, Oswald-Mammosser M, Mettauer B, Geny B, Lonsdorfer J (2000) A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the ''direct'' Fick method. Eur J Appl Physiol 85:313–320

Dempsey JA, Hanson PG, Pegelow D, Claremont A, Rankin J (1982) Limitations to exercise capacity and endurance: pulmonary system. Can J Appl Sport Sci 7:4–13

di Prampero PE, Ferretti G (1990) Factors limiting maximal oxygen consumption in humans. Respir Physiol 80:113–27

Ekblom B, Huot R, Stein EM, Thorstensson AT (1975) Effect of changes in arterial oxygen content on circulation and physical performance. J Appl Physiol 39:71–75

Fajac J, Texereau V, Rioval V, Dessanges J-F, Dinh-Xuan AT, Dall'Ava-Santucci J (1998) Blood gas measurement during exercise: a comparative study between arterialized earlobe sampling and direct arterial puncture in adults. Eur Respir J 11:712–715

Ferretti G, Moia C, Thomet JM, Kayser B (1997) The decrease of maximal oxygen consumption during hypoxia in man: a mirror image of the oxygen equilibrium curve. J Physiol 498:231–237

Fulco CS, Rock PB, Cymerman A (1998) Maximal and submaximal exercise performance at altitude. Aviat Space Environ Med 69:793–801

Gore CJ, Hahn AG, Scroop GC, Watson DB, Norton KI, Wood RJ, Campbell DP, Emonson DL (1996) Increased arterial desaturation in trained cyclists during maximal exercise at 580 m altitude. J Appl Physiol 80:2204–2210

Hartley LH, Vogel JA, Landowne M (1973) Central, femoral, and brachial circulation during exercise in hypoxia. J Appl Physiol 34:87–90

Hillier SC, Graham JA, Hanger CC, Godbey PS, Glenny RW, Wagner WW (1997) Hypoxic vasoconstriction in pulmonary arterioles and venules. J Appl Physiol 82:1084–1090

Hogan MC, Roca J, Wagner PD, West JB (1988) Limitation of maximal O_2 uptake and performance by acute hypoxia in dog muscle in situ. J Appl Physiol 65:815–821

Hogan MC, Roca J, West JB, Wagner PD (1989) Dissociation of maximal O_2 uptake from O_2 delivery in canine gastrocnemius in situ. J Appl Physiol 66:1219–1226

Hopkins SR, Bogaard HJ, Niizeki K, Yamaya Y, Ziegler MG, Wagner PD (2003) Beta-adrenergic or parasympathetic inhibition, heart rate and cardiac output during normoxic and acute hypoxic exercise in humans. J Physiol 15:605–616

Horstman D, Weiskopf R, Jackson RE (1980) Work capacity during 3-wk sojourn at 4,300 m: effects of relative polycythemia. J Appl Physiol 49:311–318

Hughes RL, Clode M, Edwards RHT, Goodwin TJ, and Jones NL (1968) Effect of inspired O_2 on cardiopulmonary and metabolic responses to exercise in man. J Appl Physiol 24:336–347

Lamberto C, Nunes H, Le Toumelin P, Duperron F, Valeyre D, Clerici C (2004) Membrane and capillary blood components of diffusion capacity of the lung for carbon monoxide in pulmonary sarcoidosis: relation to exercise gas exchange. Chest 125:2061–2068

Lawler J, Power SK, Thompson D (1988) Linear relationship between $\dot{V}O_{2max}$ and $\dot{V}O_{2max}$ decrement during exposure to acute hypoxia. J Appl Physiol 64:1486–1492

Martin D, O'Kroy J (1993) Effects of acute hypoxia on the $\dot{V}O_{2max}$ of trained and untrained subjects. J Sports Sci 11:37–42

McGuire BJ, Secomb TW (2004) Theoretical predictions of maximal oxygen consumption in hypoxia: effect of transport limitations. Resp Physiol Neurobiol 143:87–97

Peltonen JE, Tikkanen HO, Rusko HK (2001) Cardiorespiratory responses to exercise in acute hypoxia, hyperoxia and normoxia. Eur J Appl Physiol 85:82–88

Powers SK, Dodd S, Lawler J, Landry G, Kirtley M, McKnight T, Grinton S (1988) Incidence of exercise induced hypoxemia in elite endurance athletes at sea level. Eur J Appl Physiol Occup Physiol 58:298–302

Richalet J-P, Kéromès A, Dersch B, Corizzi F, Mehdioui H, Pophillat B, Chardonnet H, Tassery F, Herry J-P, Rathat C, Chaduteau C, Darnaud B (1988) Caractéristiques physiologiques des alpinistes de haute altitude. Sci Sports 3:89–108

Richard R, Lonsdorfer-Wolf E, Charloux A, Doutreleau S, Buchheit M, Oswald-Mammosser M, Lampert E, Mettauer B, Geny B, Lonsdorfer J (2001) Non-invasive cardiac output evaluation during a maximal progressive exercise test, using a new impedance cardiograph device. Eur J Appl Physiol 85:202–207

Riley R, Lilienthal J, Proemmel D, Frankee R (1946) On the determination of the physiologically effective pressure of oxygen and carbon dioxide in alveolar air. Am J Physiol 147:191–198

Robergs RA, Quintana R, Parker DL, Frankel CC (1998) Multiple variables explain the variability in the decrement in $\dot{V}O_{2max}$ during acute hypobaric hypoxia. Med Sci Sports Exerc 30:869–879

Roca J, Hogan MC, Story D, Bebout DE, Haab P, Rodriguez R, Ueno O, Wagner PD (1989) Evidence for tissues diffusion limitation of $\dot{V}O_{2max}$ in normal humans. J Appl Physiol 67:291–299

Roca J, Agusti AGN, Alonso A, Poole DC, Viegas C, Barbera JA, Rodriguez-Roisin R, Ferrer A, and Wagner PD (1992) Effects of training on muscle O_2 transport at $\dot{V}O_{2max}$. J Appl Physiol 65:1067–1076

Saltin B, Calbet JAL (2006) Point: in health and in normoxic environment $\dot{V}O_{2max}$ is limited primarily by cardiac output and locomotor muscle blood flow. J Appl Physiol 100:744–745

Squires RW, Buskirk ER (1982) Aerobic capacity during acute exposure to simulated altitude, 914 to 2286 meters. Med Sci Sports Exerc 14:36–40

Stenberg J, Ekblom B, Messin R (1966) Hemodynamic response to work at simulated altitude, 4000 m. J Appl Physiol 21:1589–1594

Terrados N, Mizuno M, and Andersen H (1985) Reduction in maximal oxygen uptake at low altitudes, role of training status and lung function. Clin Physiol 5(suppl. 3):75–79

Torre-Bueno JR, Wagner PD, Saltzman HA Gale GE, and Moon RE (1985) Diffusion limitation in normal humans during exercise at sea level and simulated altitude. J Appl Physiol 58:989–995

Wagner PD (1982) Influence of mixed venous PO_2 on diffusion of O_2 across the pulmonary blood: gas barrier. Clin Physiol 2: 105–115

Wagner PD (1988) An integrated view of the determinants of maximal oxygen uptake. Adv Exp Med Biol 227:245–256

Wagner PD (1993) Algebraic analysis of the determinants of VO_{2max}. Respir Physiol 93:221–37

Wagner PD (2006) Counterpoint: in health and in normoxic environment $\dot{V}O_{2max}$ is not limited primarily by cardiac output and locomotor muscle blood flow. J Appl Physiol 100:745–748

Wagner PD, Gale GE, Moon RE, Torre-Bueno JR, Stolp BW, Saltzman A (1986) Pulmonary gas exchange in humans exercising at sea level and simulated altitude. J Appl Physiol 61:260–270

Welsman J, Bywater K, Farr C, Welford D, Armstrong N (2005) Reliability of peak VO(2) and maximal cardiac output assessed using thoracic bioimpedance in children. Eur J Appl Physiol 94:228–34

Woorons X, Mollard P, Lamberto C, Letournel M, Richalet JP (2005) Effect of acute hypoxia on maximal exercise in trained and sedentary women. Med Sci Sports Exerc 37:147–154