Second generation Tibetan lowlanders acclimatize to high altitude more quickly than Caucasians

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Tibetan highlanders develop at altitude peak aerobic power levels ($\dot{V}_{O_2peak}$) close to those of Caucasians at sea level. In order to establish whether this feature is genetic and, as a consequence, retained by Tibetan lowlanders, altitude-induced changes of peak aerobic performance ($\Delta\dot{V}_{O_2peak}$) were assessed in four groups of volunteers with different ethnic, altitude exposure and fitness characteristics, i.e. eight untrained second-generation Tibetans (Tib 2) born and living at 1300 m; seven altitude Sherpas living at ∼2800–3500 m; and 10 untrained and five trained Caucasians. Measurements were carried out at sea level or at Kathmandu (1300 m, Nepal) (PRE), and after 2–4 (ALT1), 14–16 (ALT2), and 26–28 (ALT3) days at 5050 m. At ALT3, $\Delta\dot{V}_{O_2peak}$ of untrained and trained Caucasians was –31% and –46%, respectively. By contrast, $\Delta\dot{V}_{O_2peak}$ of Tib 2 and Sherpas was –8% and –15%, respectively. At ALT3, peak heart rate (HR_{peak}) of untrained and trained Caucasians was 148 ± 11 and 149 ± 7 beats min^{-1}, respectively; blood oxygen saturation at peak exercise (S_{aO_2peak}) was 76 ± 6% and 73 ± 6%, and haemoglobin concentration ([Hb]) was 19.4 ± 1.0 and 18.6 ± 1.2 g dl^{-1}, respectively. Compared to Caucasians, Tib 2 and Sherpas exhibited at ALT3 higher HR_{peak} (179 ± 9 and 171 ± 4 beats min^{-1}, $P < 0.001$), lower [Hb] (16.6 ± 0.6 and 17.4 ± 0.9 g dl^{-1}, respectively, $P < 0.001$), and slightly but non-significantly greater average S_{aO_2peak} values (82 ± 6 and 80 ± 7%). The above findings and the time course of adjustment of the investigated variables suggest that Tibetan lowlanders acclimatize to chronic hypoxia more quickly than Caucasians, independent of the degree of fitness of the latter.

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As is well known, with increasing altitude, peak aerobic power ($\dot{V}_{O_2peak}$) of acclimatized lowlanders undergoes a progressive decrease as a consequence of the decline of barometric pressure and of oxygen partial pressure in inspired air. At any given altitude, however, the percentage reduction of $\dot{V}_{O_2peak}$ compared to sea level control values ($\Delta\dot{V}_{O_2peak}$,%), varies widely among individuals (Cerretelli & Hoppeler, 1996). Such variability appears to be mainly related to the extent of acclimatization and to the degree of fitness. A *prolonged sojourn* at very high altitude (>5500 m) may affect $\dot{V}_{O_2peak}$ of lowlanders both positively, by the increase of blood O_2 carrying capacity (Grassi *et al.* 1996) and negatively, as a consequence of a progressive reduction of muscle mass (Cerretelli, 1976) and, possibly, of muscle deterioration (Martinelli *et al.* 1990). If the duration of the exposure is long enough (years) and altitude does not exceed ∼4000 m, developmental adaptation may occur (Moore, 2001) allowing a progressive recovery of the $\dot{V}_{O_2peak}$ towards levels only slightly lower than those found at sea level in age-, fitness- or training-matched individuals (Frisancho *et al.* 1973; Greska *et al.* 1985; Sun *et al.* 1990; Niu *et al.* 1995; Chen *et al.* 1997). With regard to *fitness*, in acute hypoxia, the peak aerobic power reduction was found to be greater in physically active than in inactive Caucasians (Lawler *et al.* 1988; Shephard *et al.* 1988; Martin & O'Kroy, 1993; Koistinen *et al.* 1995) as a consequence, among others, of a greater lung diffusion limitation (Dempsey *et al.* 1984; Dempsey & Wagner, 1999). Also in subchronic (Young *et al.* 1985) and chronic (Marzorati *et al.* 1995) hypoxia, there are hints that trained individuals may be more penalized in terms of $\Delta\dot{V}_{O_2peak}$ than untrained subjects.

Compared to acclimatized lowlanders and even Andean populations, altitude Tibetans exhibit at peak exercise

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Table 1. Age, height, body mass, body mass index (BMI) and blood haemoglobin concentration ([Hb]) of 2nd generation Tibetan lowlanders (Tib 2), altitude Sherpas (Sh), untrained (UT) and trained (T) Caucasians in control conditions (PRE) and after 26–28 days at 5050 m (ALT3)

		Tibetans	Sherpas	Caucasians	Caucasians
n		8	7	10	5
Age (year)		20 ± 2	25 ± 2	34 ± 7*§	32 ± 4*§
Heigth (cm)		170 ± 8	169 ± 6	179 ± 9	173 ± 1
Body mass (kg)	PRE	57.3 ± 8.5	54.5 ± 4.4	82.8 ± 12.5*§	65.9 ± 5.6†
	ALT3	57.7 ± 7.7	54.7 ± 3.9	76.6 ± 14.2*§[a]	63.7 ± 5.2
BMI (kg m^{-2})	PRE	19.8 ± 1.7	19.1 ± 0.9	25.9 ± 3.7*§	21.9 ± 1.7†
	ALT3	20.0 ± 1.6	19.1 ± 0.8	23.9 ± 3.9	21.2 ± 1.6
[Hb] (g dl^{-1})	PRE	13.5 ± 1.3	16.8 ± 0.8*	15.3 ± 1.0*	14.9 ± 0.9§
	ALT3	16.6 ± 0.6[a]	17.4 ± 0.9	19.4 ± 1.0*§[a]	18.6 ± 1.2*[a]

Values are means ± S.D. Significantly different from *Tib 2, §Sh, and †UT.[a] $P < 0.05$ when comparing PRE and ALT3.

peculiar adaptive features, such as higher arterial O_2 saturation (Zhuang *et al.* 1996) and heart rate values (Niu *et al.* 1995), and absolute $\dot{V}_{O_2peak}$ levels (Sun *et al.* 1990; Niu *et al.* 1995; Chen *et al.* 1997) close to those found in Caucasians at sea level. These findings, along with a less pronounced polycythemic response (Beall *et al.* 1998), a reduced hypoxic pulmonary vasoconstriction (Groves *et al.* 1993), and a lower prevalence of chronic mountain sickness (Moore *et al.* 1998), suggest that in altitude Tibetans the pattern of adaptation to chronic hypoxia is different compared to that of any other population.

The present study was designed primarily to establish whether resistance to hypoxia and, particularly the greater aerobic working capacity found in altitude Tibetans has a genetic basis. Should this be the case, Tibetan lowlanders born with the genetic adaptations of their ancestors, i.e. long-term processes occurring over generations (Moore, 2001), could be expected to acclimatize to high altitude more quickly than Caucasians. As an additional aim, we investigated the role of aerobic fitness, independent of ethnicity, on the preservation of peak aerobic performance at altitude. To achieve these aims, the respiratory and cardiovascular responses to peak exercise, particularly the altitude-induced decrease of $\dot{V}_{O_2peak}$ ($\Delta\dot{V}_{O_2peak}$) were assessed in Tibetans with different altitude exposure history and in Caucasian lowlanders with different levels of aerobic fitness, following an identical (26–28 days) altitude (5050 m) exposure protocol.

Methods

Subjects

The study was conducted, over several years, on a total of 30 male subjects with different characteristics, as follows.

Eight second-generation Tibetan lowlanders (Tib 2), born and living in Kathmandu (Nepal, 1300 m), offspring of migrants from the Tibetan plateau (3000–4500 m). None of them had ever been at altitudes above 2000 m for longer than 1 day. They frequently rode bicycles for transportation but were not engaged in any specific endurance training programme.

Seven Sherpas (Sh). Based on their genetic background, Sherpas are Tibetans born in, and lifelong residents of, the Solu Khumbu region (2800–3500 m). Our subjects, recruited among the porters of an expedition, were involved for a few weeks in house-keeping tasks at the Pyramid-laboratory at 5050 m. Assuming adaptation and full acclimatization to this altitude they were chosen as the reference group for comparison with Tibetan lowlanders.

Ten untrained Caucasian lowlanders (UT).

Five trained Caucasian lowlanders (T), running or cycling, on average, 4–8 h per week.

None of the Caucasian subjects were exposed to altitudes above 3000 m in the preceding year, and above 1200 m for 3 months before control test.

Age, anthropometrical characteristics and blood haemoglobin concentration of the subjects are given in Table 1. They underwent a preliminary clinical screening which included history taking, physical examination and resting ECG. All were highly motivated and quite cooperative. They were informed about the experimental procedure and gave consent to participate in the study, which was carried out in accordance with the principles outlined in the Declaration of Helsinki (2000) of the World Medical Association. The study was approved by the ethical committees and research review boards of the National Research Council (Milan, Italy), the Royal Nepal Academy of Science and Technologies (RONAST) and the Royal Nepal Ministry of Health (Kathmandu, Nepal).

Testing sequence

Figure 1 indicates the altitude profile and summarizes the sequence of the testing sessions. Control metabolic measurements (PRE) on Caucasians were carried out in Milan (Italy, 122 m) 10–15 days before departure to Nepal. The same data were adopted also at Kathmandu (1300 m), based on the established consensus that $\dot{V}_{O_2 peak}$ of non-athletic subjects is not affected by altitudes below 1500 m (Terrados *et al.* 1985; Gore *et al.* 1996). Control measurements on Tib 2 were performed in Kathmandu. All subjects flew from Kathmandu to Lukla (2850 m) and reached Lobuche (5050 m) in the Khumbu Valley after a 7-day trek. Subjects walked 3–5 h daily at a moderate pace carrying light loads. Two days were allowed at 3800 and 4200 m, respectively, for rest and acclimatization. Sherpas reached Lukla from their native villages and thereafter followed the same walking schedule to Lobuche as did Caucasians and Tib 2. All groups, including Sherpas, stayed 26–28 days at 5050 m. Altitude measurements were carried out in a permanent research station (the Ev-K2-CNR Pyramid-Laboratory located at 5050 m, at ~425 mmHg barometric pressure), equipped with stabilized electrical supply powered by a water turbine. Temperature inside the laboratory ranged from 17 to 22°C. Drinks and a wide variety of palatable food were freely available.

Caucasians (UT and T) and Tib 2 underwent measurements 2–4 (ALT1), 14–16 (ALT2), and 26–28 days (ALT3) after arrival at the Pyramid-Laboratory. During this period T kept active walking in the neighbourhood or exercising on a bicycle ergometer daily for about 1 h. Being lifelong altitude residents, Sherpas were tested only at the end of the sojourn (ALT3). After completion of the ALT3 session, Tib 2 repeated the test in acute hypobaric normoxia (ALT3-O_2) breathing a humidified O_2-enriched mixture (~40% O_2 in N_2). Sherpas were transferred by helicopter to Kathmandu where control measurements (PRE, see Fig. 1) were performed within 1–2 days. This procedure is necessarily different from that adopted for the other investigated groups, but it represents the only possible basis for differential metabolic measurements as a function of altitude.

Experimental procedure

Before performing the test, enough time was allowed for each subject to become familiar with the equipment, the testing procedure, and, particularly for Sherpas, with the use of the bicycle ergometer. A graded incremental exercise on an electrically braked, carefully calibrated bicycle ergometer (Cardioline STS-3, Remco, Italy) was adopted to determine peak aerobic power ($\dot{V}_{O_2 peak}$). After a 5-min period at rest, subjects performed a 4-min constant-load warming-up (30–90 watts, W, depending on altitude, age, body mass and fitness). Subsequently, the exercise workload was increased stepwise by 30 W every 3 min up to voluntary exhaustion. During the test, the subjects kept a constant pedalling rate (~60 r.p.m.) with the aid of a digital display. Exhaustion was defined as the inability to keep the imposed rate for longer than 30 s.

Gas exchange, heart rate and haemoglobin

A computerized O_2–CO_2 analyser–flowmeter combination (Vmax 2900, SensorMedics, Yorba Linda, CA, USA) was used for breath-by-breath assessment of tidal volume (V_T), pulmonary ventilation ($\dot{V}_E$) and gas exchange ($\dot{V}_{O_2}$, $\dot{V}_{CO_2}$). V_T and $\dot{V}_E$ were calculated by integration of the flow tracings recorded at the mouth of the subject by means of a pair of heated stainless steel wires (Mass Flow Sensor). Volume and gas analyser calibrations were performed prior to each measurement using a 3-litre syringe (Hewlett Packard 14278B), at three different flow rates, and by means of gas mixtures of known composition, respectively. Heart rate (HR) from ECG, and the arterialized blood oxygen saturation (S_{aO_2}) by earlobe pulse oximetry (Biox 3740, Pulse Oximeter, Ohmeda, Denver, CO, USA) were monitored throughout the tests.

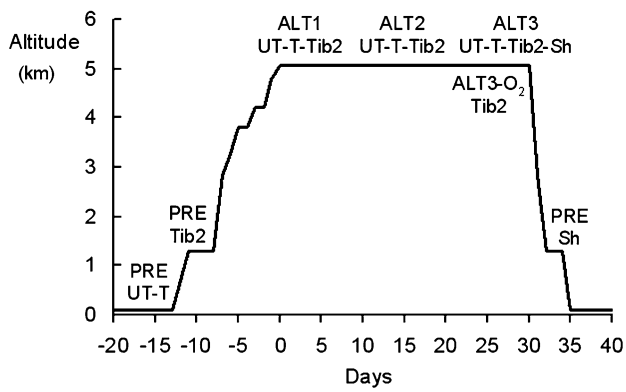

Figure 1. Altitude profile and the sequence of testing sessions for untrained (UT) and trained (T) Caucasians, and for Tibetan lowlanders (Tib 2) and Sherpas (Sh)

Untrained and trained Caucasians underwent control measurements (PRE) at sea level. The same data were adopted also at 1300 m, based on the observation that $\dot{V}_{O_2 peak}$ of sedentary subjects is not affected by altitudes below 1500 m (Terrados *et al.* 1985; Gore *et al.* 1996). Control measurements (PRE) in Tibetan lowlanders were performed at 1300 m. Experiments were carried out 2–4 (ALT1), 14–16 (ALT2), and 26–28 (ALT3) days after arrival at the Pyramid-Laboratory. At ALT3, Tibetan lowlanders repeated the test also in acute hypobaric normoxia (ALT3-O_2). At altitude, Sherpas underwent experiments only on one occasion (ALT3) and thereafter they were brought and tested at 1300 m (PRE).

Table 2. Resting oxygen consumption ($\dot{V}_{O_2}$), gas exchange ratio (R), pulmonary ventilation ($\dot{V}_E$), heart rate (HR) and arterial oxygen saturation (S_{aO_2}) of 2nd generation Tibetan lowlanders (Tib 2), altitude Sherpas (Sh) untrained (UT) and trained (T) Caucasians in control conditions (PRE) and throughout altitude exposure (ALT1, ALT2, ALT3 and ALT3-O_2)

		Tibetans (Tib 2)	Sherpas (Sh)	Caucasians (UT)	Caucasians (T)
$\dot{V}_{O_2}$ (ml kg^{-1} min^{-1})	PRE	4.3 ± 0.7	5.2 ± 0.9	3.7 ± 0.4§	4.3 ± 0.4
	ALT1	4.6 ± 0.5	—	4.2 ± 0.9	4.5 ± 1.3
	ALT2	4.5 ± 0.5	—	3.9 ± 0.5	4.1 ± 1.1
	ALT3	5.4 ± 0.6^{a}	5.1 ± 1.0	4.4 ± 0.8	4.5 ± 0.6
	ALT3-O_2	5.3 ± 1.0^{a}	—	—	—
R	PRE	0.99 ± 0.07	0.94 ± 0.05	0.84 ± 0.12*	0.79 ± 0.10*§
	ALT1	0.91 ± 0.15	—	0.83 ± 0.13	0.86 ± 0.16
	ALT2	0.98 ± 0.08	—	0.91 ± 0.12	0.98 ± 0.19
	ALT3	1.02 ± 0.09	0.98 ± 0.06	0.84 ± 0.12*§	0.88 ± 0.08
	ALT3-O_2	0.75 ± 0.12^{abcd}	—	—	—
$\dot{V}_E$ (l min^{-1})	PRE	12.8 ± 1.4	13.5 ± 2.0	9.2 ± 1.2*§	8.2 ± 1.8*§
	ALT1	15.5 ± 2.8^{a}	—	17.3 ± 7.6^{a}	14.4 ± 3.7^{a}
	ALT2	15.7 ± 2.5^{a}	—	16.7 ± 3.0^{a}	15.2 ± 2.9^{a}
	ALT3	18.3 ± 1.2 ^{abc}	15.3 ± 3.2	16.4 ± 3.7^{a}	14.2 ± 3.1^{a}
	ALT3-O_2	16.0 ± 3.0^{a}	—	—	—
HR (beats min^{-1})	PRE	81 ± 12	70 ± 12	78 ± 12	58 ± 3*†
	ALT1	95 ± 16	—	92 ± 10^{a}	80 ± 19
	ALT2	105 ± 9^{a}	—	87 ± 6*	78 ± 8*
	ALT3	93 ± 8	87 ± 9^{a}	96 ± 13^{a}	79 ± 12
	ALT3-O_2	92 ± 10	—	—	—
S_{aO_2} (%)	PRE	97.5 ± 1.1	97.9 ± 0.9	97.3 ± 1.5	96.5 ± 0.7
	ALT1	89.1 ± 2.5^{a}	—	82.5 ± 7.5^{a}	84.1 ± 5.0^{a}
	ALT2	91.0 ± 2.2^{a}	—	84.4 ± 6.2^{a}	85.9 ± 4.7
	ALT3	91.6 ± 3.5^{a}	89.0 ± 3.0^{a}	84.6 ± 5.0*^{a}	84.0 ± 3.6*^{a}
	ALT3-O_2	97.6 ± 1.2^{bcd}	—	—	—

Values are means ± S.D. Significantly different from *Tib 2, §Sh, and †UT. Significantly different from ^{a}PRE, ^{b}ALT1, ^{c}ALT2 and ^{d}ALT3.

Blood haemoglobin concentration ([Hb]) was measured at rest on venous blood samples by a photometric method (Compur M1000, Germany).

Data analysis and statistics

Steady-state values of gas exchange, HR and S_{aO_2} were obtained by averaging the breath-by-breath or the beat-by-beat data over 30–45 s time periods, at rest, as well as at the end of each workload. Data are expressed as means ± S.D. To determine the statistical significance of differences between two means, a paired two-tailed Student's t test was performed. To check the statistical significance of differences among more than two means, a one-way or a repeated-measures analysis of variance (ANOVA) was performed, when applicable. If a significant F-value was identified, the Tukey-Kramer multiple comparison test was used. Linear least squares regression analyses were performed when applicable. The level of significance was set at $P < 0.05$. For statistical analyses a commercially available software package (InStat, Graph Pad Software, San Diego, CA, USA) was used.

Results

During altitude acclimatization, [Hb] of Tibetan lowlanders and Sherpas increased slightly, attaining at ALT3 similar levels (16.6 ± 0.6 and 17.4 ± 0.9 g dl^{-1}, respectively). By contrast, at ALT3, [Hb] of untrained and trained Caucasians was 19.4 ± 1.0 and 18.6 ± 1.2 g dl^{-1}, respectively, i.e. values significantly greater ($P < 0.05$) than those of Tibetan lowlanders and Sherpas (see Table 1).

Mean resting $\dot{V}_{O_2}$, respiratory gas exchange ratio (R), $\dot{V}_E$, HR and S_{aO_2} values of the four investigated groups of subjects before (PRE) and throughout altitude exposure (ALT1, ALT2, ALT3 and ALT3-O_2) are shown in Table 2. $\dot{V}_{O_2}$ levels were significantly ($P < 0.05$) higher in Sherpas than in the other groups only at PRE. At PRE and at ALT3 resting gas exchange ratio (R) of Tibetan lowlanders and Sherpas was close to 1, and greater than that of Caucasians. Resting PRE $\dot{V}_E$ was higher in Tibetans and Sherpas than in Caucasians ($P < 0.05$). Resting HR values did not differ among ethnic groups. Only trained Caucasians had lower HR ($P < 0.05$), particularly at PRE. Resting haemoglobin O_2 saturation values were similar among groups at PRE,

Table 3. Power output ($\dot{W}$), oxygen consumption ($\dot{V}_{O_2}$), gas exchange ratio (R), pulmonary ventilation ($\dot{V}_E$), heart rate (HR) and arterial oxygen saturation (S_{aO_2}) of 2nd generation Tibetan lowlanders (Tib 2), altitude Sherpas (Sh), untrained (UT) and trained (T) Caucasians) at peak exercise carried out in control conditions (PRE) and throughout altitude exposure (ALT1, ALT2 ALT3 and ALT3-O$_2$)

		Tibetans	Sherpas	Caucasians	Caucasians
$\dot{W}$ (W)	PRE	156 ± 25	167 ± 24	210 ± 37*	276 ± 39*§†
	ALT1	131 ± 16[a]	—	144 ± 37[a]	174 ± 25†[a]
	ALT2	130 ± 19[a]	—	158 ± 14*[a]	180 ± 24*[a]
	ALT3	146 ± 25[bc]	154 ± 21	159 ± 20[a]	173 ± 29[a]
	ALT3-O$_2$	176 ± 19[abcd]	—	—	—
$\dot{W}$ (W kg^{-1})	PRE	2.7 ± 0.3	3.1 ± 0.4	2.6 ± 0.4§	4.2 ± 0.4*§†
	ALT1	2.3 ± 0.1[a]	—	1.8 ± 0.4*[a]	2.7 ± 0.3*† [a]
	ALT2	2.3 ± 0.2 [a]	—	2.0 ± 0.4[a]	2.9 ± 0.2*† [a]
	ALT3	2.5 ± 0.3[bc]	2.8 ± 0.3	2.1 ± 0.4§	2.8 ± 0.4*†
	ALT3-O$_2$	3.1 ± 0.2 [abcd]	—	—	—
$\dot{V}_{O_2}$ (l min^{-1})	PRE	2.16 ± 0.31	2.62 ± 0.40	3.21 ± 0.54*§	3.99 ± 0.32*§†
	ALT1	1.65 ± 0.15[a]	—	1.85 ± 0.42[a]	2.08 ± 0.44[a]
	ALT2	1.71 ± 0.21[a]	—	2.00 ± 0.32[a]	2.09 ± 0.50[a]
	ALT3	2.01 ± 0.25[bc]	2.25 ± 0.21[a]	2.03 ± 0.38[a]	2.07 ± 0.24[a]
	ALT3-O$_2$	2.29 ± 0.29[bcd]	—	—	—
$\dot{V}_{O_2}$ (ml kg^{-1}min^{-1})	PRE	38.0 ± 4.6	48.9 ± 6.8*	39.0 ± 6.0§	60.7 ± 3.2*§†
	ALT1	28.7 ± 3.3[a]	—	23.0 ± 5.7[a]	33.0 ± 4.4†[a]
	ALT2	30.0 ± 3.8[a]	—	25.0 ± 2.6[a]*	32.8 ± 5.2†[a]
	ALT3	35.0 ± 3.7[bc]	41.1 ± 2.9*[a]	26.9 ± 4.5*§[a]	33.0 ± 3.7§[a]
	ALT3-O$_2$	37.4 ± 4.6[bc]	—	—	—
R	PRE	1.34 ± 0.06	0.98 ± 0.03*	1.19 ± 0.11*§	1.12 ± 0.12*
	ALT1	1.33 ± 0.18	—	1.28 ± 0.15	1.21 ± 0.06
	ALT2	1.28 ± 0.07	—	1.21 ± 0.16	1.21 ± 0.14
	ALT3	1.13 ± 0.08[ab]	0.98 ± 0.04	1.11 ± 0.16	1.14 ± 0.16
	ALT3-O$_2$	1.30 ± 0.16[d]	—	—	—
$\dot{V}_E$ (l min^{-1})	PRE	121.4 ± 20.5	93.5 ± 16.9*	122.1 ± 21.6§	135.4 ± 16.8§
	ALT1	135.6 ± 19.2	—	145.4 ± 30.9	144.3 ± 37.0
	ALT2	124.1 ± 24.5	—	152.2 ± 20.8	162.3 ± 58.9
	ALT3	121.3 ± 27.9	112.5 ± 24.0[a]	147.0 ± 32.5	150.9 ± 46.8[a]
	ALT3-O$_2$	137.4 ± 15.3	—	—	—
HR (beats min^{-1})	PRE	188 ± 13	167 ± 10*	178 ± 13	190 ± 7§
	ALT1	175 ± 8[a]	—	152 ± 15*[a]	161 ± 10[a]
	ALT2	180 ± 10	—	144 ± 10*[a]	159 ± 4*[a]
	ALT3	179 ± 9[a]	171 ± 4	148 ± 11*§[a]	149 ± 7*§[a]
	ALT3-O$_2$	182 ± 11	—	—	—
S_{aO_2} (%)	PRE	96.1 ± 1.1	96.1 ± 1.0	97.8 ± 0.5	96.1 ± 1.1
	ALT1	83.4 ± 2.8[a]	—	78.2 ± 9.4[a]	71.8 ± 7.2*[a]
	ALT2	82.3 ± 7.1[a]	—	79.7 ± 6.5[a]	75.6 ± 6.1[a]
	ALT3	81.6 ± 5.8[a]	80.0 ± 7.0[a]	76.0 ± 5.6[a]	72.7 ± 5.4[a]
	ALT3-O$_2$	97.3 ± 1.8[bcd]	—	—	—

Values are means ± S.D. Significantly different from *Tib 2, §Sh, and †UT. Significantly different from [a]PRE, [b]ALT1, [c]ALT2 and [d]ALT3.

ALT1 and ALT2. At ALT3, S_{aO_2} was significantly ($P < 0.05$) lower in untrained and trained Caucasians than in Tibetans.

Peak exercise data at PRE and during the sojourn at altitude are shown in Table 3.

Peak power output ($\dot{W}_{peak,}$W) developed by Tibetan lowlanders and Sherpas was almost independent of the environmental conditions, being only 7% and 8%, respectively, lower at ALT3 than the corresponding PRE value. By contrast, $\dot{W}_{peak}$ of untrained and trained Caucasians underwent a sizeable reduction, being 26% and 37% less at ALT3 than at PRE ($P < 0.01$).

At PRE, average $\dot{V}_{O_2peak}$ values of Tibetan lowlanders and untrained Caucasians were similar (38.0 ± 4.6 and 39.0 ± 6.0 ml kg^{-1} min^{-1}, respectively). By contrast, trained Caucasians were characterized by the highest value (60.7 ± 3.2 ml kg^{-1} min^{-1}), whereas Sherpas' $\dot{V}_{O_2peak}$ was in-between (48.9 ± 6.8 ml kg^{-1} min^{-1}). At ALT1 and ALT2

$\dot{V}_{O_2peak}$ of the investigated groups underwent a significant decrease ($P < 0.05$) compared to PRE. At ALT3, Tibetans recovered almost entirely the PRE value (35.0 ± 3.7 ml kg^{-1} min^{-1}), wheras $\dot{V}_{O_2peak}$ of trained Caucasians dropped to 33.0 ± 3.7 ml kg^{-1} min^{-1}. Also $\dot{V}_{O_2peak}$ of Sherpas and untrained Caucasians was significantly ($P < 0.05$) reduced compared to PRE (41.1 ± 2.9 and 26.9 ± 4.5 ml kg^{-1} min^{-1}). In all conditions (from PRE to ALT3), gas exchange ratio (R) was in most cases ≥ 1, showing that all subjects had attained exhaustion.

Average $\dot{V}_{Epeak}$ of Tibetans was unaffected by altitude. At ALT3 $\dot{V}_{Epeak}$ of Tib 2 and Sherpas was similar (121.3 ± 27.9 and 112.5 ± 24.0 l min^{-1}, respectively). Average $\dot{V}_{Epeak}$ increased slightly in untrained and trained Caucasians. In the latter it was 150.9 ± 46.8 l min^{-1}, i.e significantly ($P <$ 0.05) higher than the PRE value (135.4 ± 16.8 l min^{-1}).

The HR$_{peak}$ levels of Tibetan lowlanders were slightly lower at ALT1, ALT2 and ALT3 (175 ± 8, 180 ± 10 and 179 ± 9 beats min^{-1}, respectively) than at PRE (188 ± 13 beats min^{-1}). The ALT3 value was not statistically different from that of the Sherpas (171 ± 4 beats min^{-1}). During O_2 breathing at ALT3, HR$_{peak}$ of Tibetans was similar to the value found at PRE. By contrast, at ALT1, HR$_{peak}$ of untrained and trained Caucasians decreased significantly compared to PRE levels, on average, from 178 ± 13 to 151 ± 15 and from 190 ± 7 to 161 ± 10 beats min^{-1}, respectively. Thereafter, HR$_{peak}$ kept further decreasing and attained 148 ± 11 and 149 ± 7 beats min^{-1}, respectively, at ALT3. HR$_{peak}$ of Tibetan lowlanders during the sojourn was always significantly ($P < 0.01$) higher than the corresponding values for untrained and trained Caucasians.

At peak exercise, average S_{aO_2} (S_{aO_2peak}) of each group was significantly lower during the sojourn at 5050 m than during the control tests (PRE). No differences were found from ALT1 to ALT3. At ALT1, average S_{aO_2peak} of Tib 2 (83 ± 3%) was significantly ($P < 0.05$) higher than that of trained Caucasians (72 ± 7%).

The percentage change of peak oxygen consumption (ml kg^{-1} min^{-1}) compared to PRE values ($\Delta\dot{V}_{O_2peak}$) of the investigated groups during the exposure to 5050 m is shown in Fig. 2. In Tib 2 at ALT1, $\Delta\dot{V}_{O_2peak}$ was −24.4 ± 6.3% ($P < 0.001$). However, in the course of the sojourn, $\dot{V}_{O_2peak}$ kept increasing steadily and at ALT3 it was not significantly different from the PRE value (∼−8%) and from the value determined during acute normoxia at ALT3 (ALT3-O_2, 37.4 ± 4.6 ml kg^{-1} min^{-1}). Similarly to Tibetans, untrained (UT) and trained (T) Caucasians underwent the greatest $\Delta\dot{V}_{O_2peak}$ (−40.9 ± 8.9% and −45.4 ± 6.3%, respectively) ($P < 0.001$) at ALT1. At ALT2, $\dot{V}_{O_2peak}$ of UT started recovering slightly, although non-significantly, whereas it did not change in T. At ALT3, $\Delta\dot{V}_{O_2peak}$ average values of untrained and trained Caucasians were −30.7 ± 9.3% and −45.7 ± 3.5%, respectively. During acclimatization $\Delta\dot{V}_{O_2peak}$ was significantly ($P < 0.05$) greater in Caucasians than in Tib 2. At ALT3, $\Delta\dot{V}_{O_2peak}$ of Sherpas was ∼−15%, i.e. slightly higher ($P < 0.05$) than the value for Tib 2.

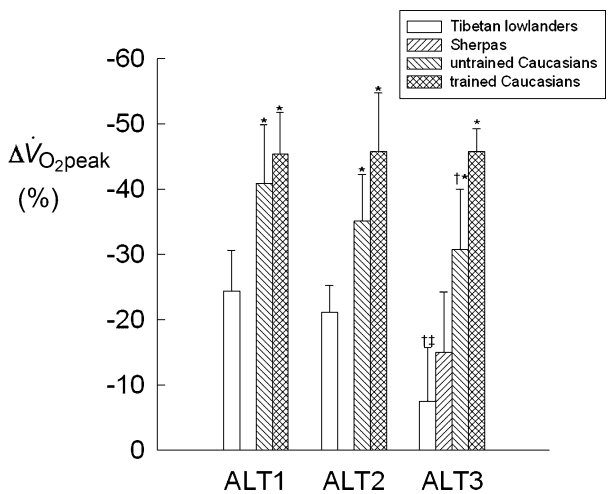

Figure 2. Time course of the percentage change of peak oxygen consumption expressed per kg of body mass ($\Delta\dot{V}_{O_2peak}$, the PRE value made equal to 0) of Tibetan lowlanders, Sherpas, and untrained and trained Caucasians during the sojourn at 5050 m
*$P < 0.05$ when comparing Caucasians with Tibetans and Sherpas at a given condition. †,‡$P < 0.05$ when comparing ALT3 with ALT1 and ALT2, respectively.

Discussion

The present study was designed to investigate the main metabolic, respiratory, and cardiovascular responses to peak exercise of subjects with different ethnic background, altitude exposure history and training conditions, in the course of a standardized sojourn at 5050 m. To the authors' knowledge this is the first comparative study carried out on homogeneous groups of selected subjects, in identical environmental conditions, using the same protocols and experimental set-up, i.e. eliminating most of the common confounding factors.

Two findings stemming from this investigation are novel. The first is that Tibetan lowlanders (Tib 2) never exposed to high altitude before, compared to untrained and trained Caucasians, were able to retain almost entirely their PRE $\dot{V}_{O_2peak}$ ($\Delta\dot{V}_{O_2peak}$: −8% *versus* −30% and −45%, respectively). The second is that, within the investigated ethnic groups (Caucasians and Tibetans), subjects with higher aerobic power in control conditions lost at ALT3 a greater fraction of their PRE $\dot{V}_{O_2peak}$. This finding may explain in part the dissociation found in elite Caucasian mountaineers between climbing performance and sea-level $\dot{V}_{O_2peak}$. Indeed, one of the greatest climbers of the last century (Reinhold Messner), the first man ever to reach the summit of Mt Everest (8848 m) without supplementary oxygen, was characterized at sea level by a $\dot{V}_{O_2peak}$ of only 49 ml kg^{-1} min^{-1} (Oelz *et al.* 1986).

Respiratory, metabolic and heart rate measurements

At PRE, resting $\dot{V}_{O_2}$ level appears to be significantly higher in Sherpas than in all the other groups (see Table 2). Excitement and/or metabolic alterations from changing nutritional habits might be at the basis of this unexpected finding. Both Tibetan groups were characterized by higher resting $\dot{V}_E$ levels compared to Caucasians. These results are most probably explained by the discomfort due to breathing through a mouthpiece. Nevertheless, Sherpas, like acclimatized Caucasians, might have been characterized also by a persistent adaptation-induced hyperventilation, at least in the early phase of acute normoxia (Weil, 1991). It may also be noticed that at PRE and ALT3 resting gas exchange ratio (R) of Tibetan lowlanders and Sherpas is close to 1, being greater than in Caucasians. Higher R levels, when reflecting higher respiratory quotients, may be advantageous for Tibetans and Sherpas, particularly at altitude. In fact, for any given CO_2 tension, high R would be accompanied by higher O_2 tension in the alveolar air, thus enhancing O_2 diffusion through the alveolar–capillary barrier (Ward *et al.* 1990). Resting HR values at PRE were similar among groups. Only trained Caucasians had significantly lower resting HR and this was likely the result of their training history.

As shown in Table 3, average peak aerobic power was significantly ($P < 0.05$) different in Tib 2 and Sherpas both at 1300 m (38 *versus* 49 ml kg^{-1} min^{-1}) and at 5050 m (35 *versus* 41 ml kg^{-1} min^{-1}), respectively. This finding reflects the better fitness of Sherpas, who were more active than Tibetan lowlanders.

Relationships between $\Delta\dot{V}_{O_2peak}$ at altitude and control PRE $\dot{V}_{O_2peak}$ values

As shown in Fig. 2, after 26–28 days at 5050 m Tibetan lowlanders, differently from Caucasians, recovered almost entirely their PRE $\dot{V}_{O_2peak}$. This feature may be considered the result of a genetic adaptation enhancing acclimatization. In fact, as shown by Sun *et al.* (1990) and Niu *et al.* (1995), at 3680 m the recovery of sea level $\dot{V}_{O_2peak}$ by Han individuals without such adaptation may take years.

In Fig. 3, individual $\Delta\dot{V}_{O_2peak}$ data of all subjects at ALT3 are plotted *versus* the corresponding $\dot{V}_{O_2peak}$ control values (PRE). Two distinct linear functions can be identified by interpolating data from untrained and trained Caucasians (A; $r = 0.71$; $P < 0.01$), and from Tibetan lowlanders and Sherpas (B; $r = 0.74$; $P < 0.001$), respectively. Function B is parallel, down-shifted, and significantly different ($P <$ 0.05) from A. It appears that the percentage loss of $\dot{V}_{O_2peak}$ at altitude ($\Delta\dot{V}_{O_2peak}$, %) is positively correlated, both in Caucasians (UT and T) and in Tibetans (Tib 2 and Sh) with the $\dot{V}_{O_2peak}$ control values (PRE). The greater loss of $\dot{V}_{O_2peak}$ in trained compared with untrained individuals might be the consequence of the greater impairment of O_2–blood equilibration due to a shorter red blood cell alveolar–capillary transit time (Dempsey *et al.* 1984; Hopkins *et al.* 1996; Dempsey & Wagner, 1999). The vertical difference between functions A and B, i.e. an index of the capacity of Tibetans to preserve at altitude a greater fraction of their control PRE $\dot{V}_{O_2peak}$ compared to Caucasians, probably depends on ethnic characteristics. These novel findings raise a major issue concerning the mechanism by which Tibetans preserve more of their PRE $\dot{V}_{O_2peak}$ at altitude.

Factors allowing Tibetans to preserve their peak aerobic power at altitude

Determinants of $\dot{V}_{O_2peak}$. As is well known, in Caucasians at sea level $\dot{V}_{O_2peak}$ depends mainly (∼70%) on peak cardiac output ($\dot{Q}_{peak}$). The latter is the major determinant of the maximum circulatory convective O_2 flow, i.e. the product of $\dot{Q}_{peak}$ and arterial O_2 content ($C_{aO_2} =$ [Hb] × S_{aO_2}%), to

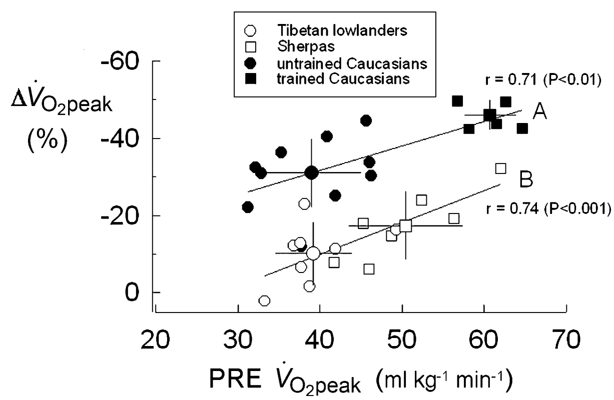

Figure 3. Individual loss of peak aerobic power expressed per kg of body mass ($\Delta\dot{V}_{O_2peak,\%}$) after 26–28 days (ALT3) at 5050 m, as a function of the corresponding PRE peak aerobic power ($\dot{V}_{O_2peak}$, ml kg^{-1}min^{-1})

Mean values ± S.D. of the 4 groups of subjects are also shown (large symbols). Continuous lines (*A* and *B*), fitted through individual values, differ significantly from each other ($P < 0.05$).

exercising muscles. In acute hypoxia the role of the cardiovascular factors tends to decrease, whereas the influence of alveolar ventilation, O_2 diffusion across the alveolar–capillary barrier and of the tissue factors (from the capillary down to the respiratory chain) progressively increases (di Prampero & Ferretti, 1990; Wagner, 1996). At altitudes above 5500 m, the weight of tissue factors, due to muscle wasting, is expected to play an even greater role, mainly in Caucasians (Martinelli *et al.* 1990; Hoppeler *et al.* 2003; Gelfi *et al.* 2004). The role of the above determinants may be different in acclimatized Tibetan lowlanders as a consequence of genetic adaptations.

Haemoglobin concentration. Tibetan lowlanders and altitude Sherpas share a low blood haemoglobin concentration. At any given altitude below 5000 m, [Hb] has generally been reported to be lower in Tibetan populations than in Andean highlanders (Beall, 2001) and in acclimatized Caucasian or Asian lowlanders. Indeed, after 26–28 days at 5050 m, [Hb] of Tib 2 and Sherpas was similar, 16.6 and 17.4 g dl^{-1}, respectively, i.e. significantly ($P < 0.05$) lower than values for acclimatized Caucasians (18.6–19.4 g dl^{-1}). Apart from the possible positive effects on the cardiac function of the concurrent drop in haematocrit and blood viscosity, low [Hb] may be advantageous for peripheral O_2 transport. In fact, as was recently shown by Calbet *et al.* (2002), leg blood flow and vascular conductance of lowlanders acclimatized to 5260 m were systematically higher when [Hb] was artificially reduced.

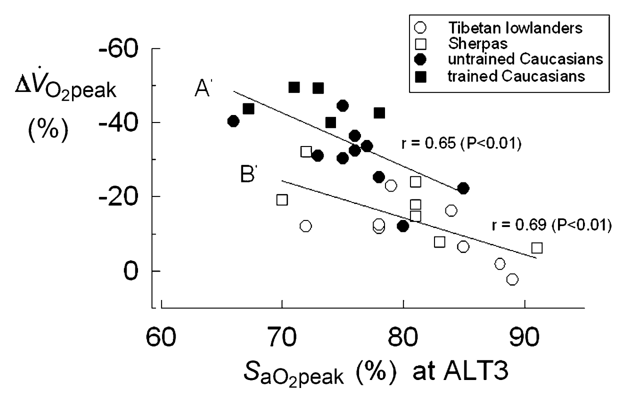

Figure 4. Individual loss of peak aerobic power expressed per kg of body mass ($\Delta\dot{V}_{O_2peak,\%}$) after 26–28 days (ALT3) at 5050 m, as a function of the corresponding value of arterial O_2 saturation ($S_{aO_2peak,\%}$) at peak exercise

Regression equations were determined for untrained and trained Caucasians (A′, $P < 0.01$) and for Tibetan lowlanders and Sherpas (B′, $P < 0.01$). The difference between the two equations is statistically significant ($P < 0.01$).

Arterial O_2 saturation. At peak exercise carried out at altitude, individual arterial O_2 saturation (S_{aO_2peak}) ranged from ∼65% to ∼90%. As shown in Fig. 4, at ALT3 most Tibetans and Sherpas were characterized by S_{aO_2peak} values higher than Caucasians. The large variability in S_{aO_2peak} is likely to be attributable to differences in lung maximum O_2 diffusing capacity ($DL_{O_2,max}$), which is usually lower in acclimatized Caucasians than in altitude natives (Wagner *et al.* 2002). Exercise gas exchange at the alveolar level, and therefore S_{aO_2}, may be less impaired in altitude Tibetans than in Caucasians by lesser extravascular accumulation of fluids in the lung (see Anholm *et al.* 1999; Cremona *et al.* 2002), reduced hypoxic pulmonary vasoconstriction (for a review, see Moore *et al.* 1998), and more limited ventilation–perfusion mismatch. Due to genetic adaptations, such characteristics might still be present in some Tibetan lowlanders, thus generating higher S_{aO_2peak} values. In fact, in the absence of a genetic adaptation, S_{aO_2peak} of acclimatized lowlanders may take years to approach the values found in altitude natives (Sun *et al.* 1990).

$\Delta\dot{V}_{O_2peak}$ values of the investigated subjects appear to be correlated also with S_{aO_2peak}. In Fig. 4, individual $\Delta\dot{V}_{O_2peak}$ values at ALT3 are plotted *versus* the corresponding S_{aO_2peak} values. Again, two linear functions can be identified interpolating the individual data of trained and untrained Caucasians (A′, $r = 0.65$; $P < 0.01$), and those of Tibetan lowlanders and Sherpas (B′, $r = 0.69$; $P < 0.01$), respectively. It appears that (i) the subjects characterized by the lowest S_{aO_2peak} are those undergoing the largest loss of $\dot{V}_{O_2peak}$ (trained Caucasians); (ii) at peak exercise, and with the same S_{aO_2peak}, Tibetans (Tib 2 and Sherpas) preserve $\dot{V}_{O_2peak}$ better than Caucasians. That is to say that S_{aO_2peak} is not the sole factor affecting Tibetans' $\dot{V}_{O_2peak}$ at altitude.

Peak heart rate and cardiac output. As shown in Table 3, following 28–30 days' altitude exposure, HR_{peak} of T and UT Caucasians decreased, on average, from ∼180–190 to ∼150 beats min^{-1}. This is likely to be a consequence of a down-regulation of β-adrenergic cardiac receptors (Richalet *et al.* 1988) and/or of enhanced parasympathetic activity (Hartley *et al.* 1974; Boushel *et al.* 2001). In this context, however, it was recently shown that parasympathetic blockade, while increasing HR_{peak}, had no effect on maximal cardiac output and exercise capacity of acclimatized lowlanders, at least up to 3800 m (Bogaard *et al.* 2002) and therefore should not influence $\dot{V}_{O_2peak}$. By contrast, HR_{peak} of acclimatized Tibetan lowlanders changed only slightly from control values, attaining, on average, ∼180 beats min^{-1}, i.e. almost the same value found during acute normoxia. The latter finding indicates that, despite the fact that they were born at low altitude, Tibetan lowlanders, as is the case for Tibetan highlanders (Zhuang *et al.* 1993) and altitude Sherpas, apparently do not undergo desensitization of β-adrenergic cardiac receptors or increase of the parasympathetic tone upon exposure to chronic hypoxia.

Cardiac output was not determined in the present study. However, it is likely that maximal O_2 convective flow ($\dot{Q}_{peak} \times C_{aO_2}$) was almost preserved in all subjects, independent of their ethnicity. In fact, it is known that at altitudes between 3800 and 5800 m, peak or near-peak $\dot{Q}$ of physically active acclimatized Caucasians (for a review see Wagner, 2000) may range from ∼14 to ∼20 l min^{-1} (Pugh, 1964; Vogel *et al.* 1967; Saltin *et al.* 1968; Cerretelli, 1976; Bogaard *et al.* 2002; Calbet *et al.* 2002), being ∼15% lower than sea level control values. Nevertheless, in acclimatized lowlanders as well as in Andean populations, the decrease of maximum convective O_2 flow, depending on the decrease of $\dot{Q}_{peak}$ is more than compensated for by a ∼30% increase in [Hb] and arterial O_2 content (Cerretelli, 1976; Calbet *et al.* 2002, 2003). On the other hand, haemoglobin O_2 affinity of acclimatized lowlanders, altitude Sherpas and Andean populations was found to be close to sea-level standards or only slightly increased (Samaja *et al.* 1979; Moore *et al.* 1992, 1998). Thus, in acclimatized lowlanders there seems to be a dissociation between the almost constant maximal O_2 delivery to the working muscles and the drop of $\dot{V}_{O_2peak}$ during exercise at altitude. Although the underlying mechanisms are still unknown, the hypothesis can be put forward that, due to high [Hb] values, a relatively lower fraction of nutritional blood flow may perfuse exercising muscles at altitude (Calbet *et al.* 2003). This may not be the case for acclimatized Tibetan lowlanders. In fact, as mentioned before, their higher HR_{peak} and lower blood viscosity are likely to favour adequate $\dot{Q}_{peak}$ values (Chen *et al.* 1997) and to increase nutritional blood flow to working muscles, respectively. The latter, along with an apparently larger oxygen extraction (Pugh, 1964) may account for the greater preservation at altitude of PRE $\dot{V}_{O_2peak}$ in acclimatized Tibetans compared to Caucasians. On the other hand, apart from a slight reduction in body weight observed in untrained Caucasians, there are no hints of structural and functional deterioration of the muscle mass after the sojourn at the Pyramid-Laboratory that could account for the loss of different fractions of PRE $\dot{V}_{O_2peak}$ in the investigated groups (Kayser *et al.* 1993). Relevant for the interpretation of the present results may be the finding that Tibetan lowlanders are characterized by smaller muscle fibre cross-sectional area than non-Tibetan controls (Kayser *et al.* 1996). Since the muscle capillary density is the same, this adaptive change may result in a shorter diffusion path for O_2 at the muscle level. The above feature may be one of the factors contributing to preserve $\dot{V}_{O_2peak}$ of Tibetan lowlanders upon hypoxia exposure.

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