

Exercise economy does not change after acclimatization to moderate to very high altitude

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For more than 60 years, muscle mechanical efficiency has been thought to remain unchanged with acclimatization to high altitude. However, recent work has suggested that muscle mechanical efficiency may in fact be improved upon return from prolonged exposure to high altitude. The purpose of the present work is to resolve this apparent conflict in the literature. In a collaboration between four research centers, we have included data from independent high-altitude studies performed at varying altitudes and including a total of 153 subjects ranging from sea-level (SL) residents to high-altitude natives, and from sedentary to world-class athletes. In study A ($n = 109$), living for 20–22 h/day at 2500 m combined with training between 1250 and 2800 m caused no differences in running economy at fixed speeds despite low typical error measurements. In study B, SL residents ($n = 8$) sojourning for 8 weeks at 4100 m and residents native to this altitude ($n = 7$) per-

formed cycle ergometer exercise in ambient air and in acute normoxia. Muscle oxygen uptake and mechanical efficiency were unchanged between SL and acclimatization and between the two groups. In study C ($n = 20$), during 21 days of exposure to 4300 m altitude, no changes in systemic or leg VO_2 were found during cycle ergometer exercise. However, at the substantially higher altitude of 5260 m decreases in submaximal VO_2 were found in nine subjects with acute hypoxic exposure, as well as after 9 weeks of acclimatization. As VO_2 was already reduced in acute hypoxia this suggests, at least in this condition, that the reduction is not related to anatomical or physiological adaptations to high altitude but to oxygen lack because of severe hypoxia altering substrate utilization. In conclusion, results from several, independent investigations indicate that exercise economy remains unchanged after acclimatization to high altitude.

The first systematic measurement of whole-body oxygen consumption during cycle ergometer exercise in high altitude dates back to the International Expedition to Chile in 1935 by Christensen (1937). In this classic study, and several subsequent studies, whole-body oxygen consumption at a given work rate was unchanged at altitude (Pugh et al., 1964; Consolazio et al., 1966; Klausen et al., 1970; Maher et al., 1974; West et al., 1983; Bender et al., 1988; Svedenhag et al., 1991; Wolfel et al., 1991; Grassi et al., 1996; Young et al., 1996; Lundby & van Hall, 2002; Calbet et al., 2003) or slightly increased (Roberts et al., 1996) at high altitude compared with sea level (SL). In support of this observation, during acute hypoxic exposure no alterations in submaximal VO_2 have been reported (Dill et al., 1966; Cerretelli et al., 1967; Hughes et al., 1968; Hogan et al., 1983). Also, studies applying intermittent hypoxic exposure

report unchanged SL submaximal VO_2 s after hypoxia (Telford et al., 1996; Levine & Stray-Gundersen, 1997; Rodriguez et al., 2000; Clark et al., 2004; Lundby et al., 2004). Recently, however, both prolonged and intermittent hypoxic exposure have been suggested to increase the mechanical efficiency of exercise when performed at SL (Green et al., 2000b; Gore et al., 2001; Katayama et al., 2003; Saunders et al., 2004). Moreover, it has also been reported that high-altitude natives have a higher mechanical efficiency compared with SL residents (Hochacka et al., 1991).

The purpose of the present study is to resolve this apparent conflict in the literature. The weaknesses of some previous studies include (1) small subject number (Green et al., 2000b; Gore et al., 2001); (2) primitive field conditions where subjects were exposed to varying altitudes for a varying amount of

time (Green et al., 2000b). During climbing expeditions, stimuli such as cold, marked changes in exercise habits, reduced availability, and different types of food, all could conceivably have altered muscle structure and function under these extraordinary conditions; (3) high oxygen requirements for a given work rate observed before altitude exposure, whereas more normal values were observed after the hypoxic exposure period (Katayama et al., 2003); and (4) intralaboratory variability in outcome, i.e., with similar study designs, efficiency either remained unchanged (Telford et al., 1996; Clark et al., 2004) or was increased (Gore et al., 2001; Saunders et al., 2004) although the studies were performed by the same research group.

The aim of the present study was to test rigorously whether chronic high-altitude exposure is accompanied by changes in muscle mechanical efficiency. We have investigated the effects of prolonged hypoxic exposure in SL residents and in high-altitude natives on O₂ consumption for a given work rate. Our data include leg and whole-body oxygen consumption both during hypoxia and acute normoxia at different altitudes. Furthermore, we have studied oxygen consumption during knee-extensor exercise. The data have been gathered in six high-altitude studies, listed ascending with altitude: (A) the 1994–2000 “live high–train low” studies by Levine and Stray-Gundersen; (B) the 2001 Danish El Alto expedition; (C) the 1987, 1988, and 1991 Pikes Peak expeditions; and (D) the 1998 Danish Chacaltaya expedition. Combining these studies give a total subject number of 153. Some of the data have been published previously, however, not with the emphasis as in the present context.

Methods

Study A: Levine and Stray-Gundersen’s “live high–train low”

The data presented here come from three independent studies performed by the investigators from 1994 to 2000. The data from the first series of studies (A1: 1994–1996) have been published in Levine & Stray-Gundersen 1997 and Levine, 2002); the data from the second study (A2: 1997) were published in Stray-Gundersen et al. (2001). The data from the third series of studies (A3: 1999–2000) have been published only in abstract form. The results for studies A1 and A3 were gathered by Levine and Stray-Gundersen in Dallas, whereas the data for study A2 were gathered in JM Stager’s laboratory at the Indiana University.

Study A1

Thirty-nine distance runners participated in these studies, which followed the same protocol. Athletes were required to be competitive at a distance between 1500 m and the marathon, and to have a recent personal best 5000 m time (or equivalent) of <16:30 for men and <18:30 for women. All subjects gave their voluntary written informed consent to a protocol approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

The study design consisted of four major phases: (1) SL lead-in phase – athletes were brought to Dallas, TX (150 m), 2–4 weeks following the spring track season, for a 2-week period of supervised training at SL, and familiarization with laboratory testing procedures. The first formal baseline set of data were obtained after this familiarization phase; (2) SL training – following the lead-in phase, athletes underwent a period of supervised training at SL. Training was carefully standardized and monitored as described previously (Levine, 1997). Repeat laboratory testing occurred during the last week at SL; and (3) Altitude training camp – following the last measurements at SL, athletes were then matched for gender, 5000 m time-trial performance, and training history into groups of three (a fourth, concurrent SL training camp control was also performed, but these data are not reported here), and then randomized (balanced randomization) to either: (1) living at moderate altitude (2500 m) and conducting all high- and low-intensity training at low altitude (1200–1400 m) – “high–low” ($n = 13$; nine males, four females). This group thus spent 20–22 h/day at moderate altitude; (2). living at moderate altitude (2500 m) and conducting all training at moderate altitude (2500–2700 m) – “high–high” ($n = 13$; nine males, four females – typical altitude training control group). This group spent 24 h/day at moderate altitude with no low-altitude exposure; or (3) living at moderate altitude (2500 m), conducting all base/low-intensity training sessions at moderate altitude (2500 m), and conducting all high-intensity training at low altitude (1200 m) – “high–high–low” ($n = 13$; nine males, four females). This group spent 22–24 h /day at moderate altitude. The training program during the field camp matched the training program at SL in Dallas, based on the same 4-week mesocycle. (4) SL testing period – tests of running economy were performed on the second day after return from altitude.

Economy evaluation

Oxygen uptake was measured using the Douglas bag method: gas fractions were analyzed by a mass spectrometer (Marquette MGA 1100, Marquette Electronics, Milwaukee, WI, USA), and ventilatory volume (VE) was measured with a Tissot spirometer (Warren & Collins Inc., Boston, MA, USA). Sub-maximal economy during flat treadmill running was estimated from the relationship between oxygen uptake and treadmill speed during 3, 5 min submaximal runs at 0% grade: 12.9, 16.1, and 19.3 km/h for men, and 12.9, 14.5, and 16.1 km/h for women. Oxygen uptake at each level was measured from a 1 min Douglas bag obtained from the third to fourth minute. The treadmill was carefully calibrated before all testing. Running economy was defined in two ways: first, as the absolute VO₂ at a common treadmill speed at 16.1 km/h. The second method used the slope of the regression relating VO₂ to treadmill speed. The typical error reported as coefficient of variation for oxygen uptake at 16.1 km/h for the athletes in this study on repeat measurement at SL was 3.2% (Hopkins, 2000). This level of precision and reproducibility is comparable with that from other laboratories that have reported a decrease in oxygen uptake after altitude exposure and have also reported a typical error of measurement (Gore et al., 2001; Saunders et al., 2004).

Study A2

Twenty-four distance runners (15 men and nine women) completed all the testing for this study. Athletes were required to be competitive at a national level in an event from the 1500 m to the marathon. All but two athletes competed in the 1997 NCAA Championships or the 1997 USA Track and Field Championships or both. The subjects gave their written consent to the study, which had received approval from the

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Institutional Review Board of the University of Texas Southwestern Medical Center.

The athletes were assessed at SL in the week before and the week after 27 days of living at 2500 m, in the same housing as the athletes for study A1. Athletes were required to perform high-intensity, high-velocity training at 1250 m. All other training took place between 1250 and 3000 m, with most of the training occurring between 2000 and 2800 m.

Treadmill assessment

After a 5 min warm up, the athletes ran at two submaximal, steady-state work rates. The first was considered equivalent to typical “base” training pace, which was set at 14.4 km/h for women and 16.1 km/h for men. The second was set at a higher velocity, at a pace equivalent to slightly slower than race pace for these athletes: at 19.3–20.1 km/h for men and 16.1 km/h for women. The same speeds were used before and after altitude exposure for all athletes. Inspired ventilation was measured by a dual thermistor flow probe (Torrent 1200, Hector Engineering, Bloomington, IN, USA), and expired gas concentrations were measured in a 5 L mixing chamber by a mass spectrometer (Marquette RMS M-100, Milwaukee, WI, USA). Heart rate was recorded at the end of each minute by telemetry (Polar, Kempele, Finland). Data were collected and displayed with the use of a data acquisition control system (Workbench for Windows 2.0, Strawberry Tree, Sunnyvale, CA, USA) sampling at 40 Hz. Values for SaO_2 , VO_2 , and VE were averaged over each minute of exercise.

Study A3

Twenty-four runners (16 men, eight women) served as the subjects for this study. The athletes were collegiate and post-collegiate competitive distance runners, who were generally equivalent to the athletes in study A1, although with a slightly faster performance criterion (recent performance of <16:00 for men, and <18:00 for women over 5000 m or the equivalent). All athletes spent 4 weeks in Dallas (150 m) for a period of familiarization and testing. Final baseline testing, which served as the primary comparison for the post-altitude exposure, occurred during the last week in Dallas. The athletes were then transported to altitude where half of them lived at 2500 m and the other half lived at 2850 m. All training occurred together, with base training between 1250 and 2800 m, and interval training exclusively at 1250 m (“high-high-low”). Post-altitude testing occurred the third day after return from altitude.

Treadmill testing was performed on the same calibrated treadmill and the same system for measuring oxygen uptake as in study A1. Submaximal oxygen uptake was measured during the fourth minute of steady-state treadmill running at 14.4 km/h for both men and women.

Study B: 2001 Danish El Alto (4100 m) expedition

These are original unpublished data. The study has been described in detail elsewhere (Lundby et al., 2004), and will only be outlined briefly here.

Subjects

Eight Danish SL residents (six males+two females) and seven high-altitude Aymara natives participated in this study.

The research protocol was approved by the Ethical Committee of Copenhagen and Frederiksbergs communities (KF11-050/01) and by El Tribunal de Honor del Colegio

Médicino Departamental La Paz, and the Ministerio de Previsión Social y Salud Pública, La Paz, Bolivia.

Protocol

After familiarization trials, $\text{VO}_{2\text{max}}$ was determined by the use of a progressive exercise protocol on a cycle ergometer (Monark 824E, Valberg, Sweden), at 80 r.p.m. Exercise was started with a 15 min warm up period of 100 W for the males and 80 W for the female and the high-altitude natives, after which the workload was increased by 40 W every 2½ min until exhaustion. $\text{VO}_{2\text{max}}$ was defined as the value obtained when an increase in exercise intensity of 40 W did not result in any further increase in O_2 uptake ($\text{VO}_{2\text{max}}$; i.e., a decrease, no change, or an increase <150 mL/min). This procedure resulted in a plateau in VO_2 in seven out of eight subjects.

Testing protocol

The SL residents were investigated in Copenhagen at SL, and about 1 week later when exposed to acute hypoxia (AH) by breathing 12.4% O_2 in N_2 (equivalent to 4100 m) from a Douglas bag (the subjects started to breathe the hypoxic gas mixture 10 min before the start of exercise). Subjects were investigated again after 2 (2 W) and 8 (8 W) weeks of altitude acclimatization to 4100 m, and the experiments were also conducted at this altitude. During these two sessions, the maximal exercise test was followed by 1½ h of supine rest, after which they repeated the incremental exercise test to exhaustion. During this test, the subjects breathed air from a cylinder containing 35% O_2 in nitrogen in order to reproduce a normoxic SL condition (barometric pressure at 4100 m \approx 470 mmHg, and this multiplied by 35% oxygen gives a PiO_2 of 165 mmHg). The high-altitude natives were investigated with the same two protocols, i.e. once in hypobaric hypoxia, and once in hyperoxic normoxia. Before exercise start, and after the 15 min warm up period, a muscle biopsy was obtained from the vastus lateralis. Also, during the entire testing, blood samples were drawn from indwelling venous and arterial femoral catheters.

Measurements

VO_2 , VCO_2 , and VE were measured on-line by the use of standard open-circuit techniques (Oxygen Analyzer S-3A/I, Ametek, Padi, PA, USA; LB-2, Beckman, Midlan, ON, Canada; VRDC/HC-1, Parvo Medics, Salt Lake City, UT, USA). Before use, the system was calibrated against two gas mixtures previously measured by the micro-Scholander method. Flow was calibrated with a 3 L syringe. Pulmonary gas exchange was measured during the entire test at 15 s intervals. Blood samples were drawn from indwelling catheters in the femoral artery and vein. Blood flow was measured by the thermodilution method. For detailed procedure description, please see Lundby et al. (2004).

Study C: the 1987, 1988, and 1991 Pikes Peak (4300 m) expeditions

The data presented here come from three independent studies performed on Pikes Peak between 1987 and 1991. Parts of the data have been published previously (Bender et al., 1988; Wolfel et al., 1991).

Subjects

Subjects for the 1987 ($n = 7$), 1988 ($n = 7$), and 1991 ($n = 6$) Pikes Peak studies (mean age = 24.2 ± 1.8 years) were

non-smoking, SL residents not involved in regular endurance training. The experimental design was similar for all three studies and was as follows: Subjects were tested at SL (Palo Alto VA Hospital – barometric pressure = 754 mmHg), within the first 4 h of arrival at 4300 m (Pikes Peak – 464 mmHg), and after 21 days of residence at the summit of Pikes Peak (463 mmHg). Subjects maintained their normal physical activity levels (as that found at SL) during the 3 weeks at 4300 m to avoid any fluctuations in exercise. Additionally, their diet was strictly regulated to avoid weight loss normally associated with prolonged stay at altitude.

Testing protocol

Submaximal exercise tests were performed at SL, within 4 h of arrival to (acute) and after 21 days of residence at high altitude (chronic). Before exercise, subjects rested quietly for 90 min seated in a chair. Subjects then performed 45 min of submaximal steady-state exercise on the bicycle ergometer at an intensity of 50% $\text{VO}_{2\text{max}}$ obtained at SL, i.e. approximately 65% of altitude $\text{VO}_{2\text{max}}$. During acute and chronic altitude exposure, an absolute exercise intensity similar to that of SL was chosen such that subjects were working at the same absolute VO_2 across all three conditions. Respiratory measurements and blood samples were collected at rest (–15 and 0 min before exercise) and at 5, 15, 30, and 45 min of exercise.

The femoral artery and vein of one leg were cannulated using standard percutaneous techniques. Arterial and venous leg PO_2 as well as oxygen content were measured independently for each blood sample (OSM 3 Hemoximeter, Radiometer Copenhagen, Copenhagen, Denmark) both at rest and during exercise. Leg VO_2 and blood flow were determined as previously described. Briefly, a 10 mL bolus of sterile saline (0 °C) was infused via the venous catheter, and flow was measured in triplicate by thermodilution using a cardiac computer (American Edwards Laboratories Model 9520, Irvine, CA, USA). Thermodilution curves were validated on a Soltec recorder (Model 8K22, San Fernando, CA, USA).

Study D: 1998 Danish Chachaltaya (5260 m) expedition.

The one-legged kicking data have not been published previously, and the bike ergometer exercise data have only been published partially (Calbet et al., 2003).

Subjects and protocol

Nine Danish lowlanders (four females and five males) participated in these studies. Their mean (\pm SE) age, height, and weight were 24.3 ± 0.5 years, 176 ± 3 cm, and 74 ± 4 kg, respectively. The subjects were informed about the procedures and risks of the study before giving written informed consent to participate as approved by the Copenhagen–Fredriksberg Ethical Committee.

This study was conducted at altitude after 9 weeks of residence at 5260 m at Mt. Chacaltaya (Bolivia). SL and AH measurements were performed in random order 6–9 months after return to Copenhagen. AH was induced by allowing subjects to breathe 10% O_2 balanced in N_2 from a Douglas bag. First subjects performed knee-extensor exercise (Andersen & Saltin, 1985) at a mean intensity of 31 W for 10 min. The average VO_2 , VCO_2 , and VE were recorded (Medical Graphics CPX, St. Paul, Minneapolis, MN, USA) during the last 4 min and were taken as a representative value of the corresponding exercise bout. An hour later, the same variables were measured during cycle ergometer exercise in upright position

at a mean intensity of 116 W. A three-lead electrocardiogram was displayed on a monitor during the exercise.

Calculations and statistics for all studies

In studies A and B, running and cycle efficiency was calculated as the slope of the regression relating work to oxygen uptake. The absolute oxygen uptake at each speed was also calculated and compared.

Differences in the measure variables were analyzed with one-way ANOVA for studies A, C, and D, and two-way ANOVA in study B, both for repeated measurements. When F was significant in the ANOVA, Student's t -test was carried out. Significance was accepted at $P < 0.05$. Values reported are mean \pm SE.

Results

Study A1: SL residents investigated at SL after exposure to 2500 m (Fig. 1)

Figure 1 shows the individual and mean group values for oxygen uptake during treadmill running at 16.1 kph before and after 4 weeks of training at SL in Dallas, and then again after 4 weeks of living at 2500 m altitude and training between 1250 and 2800 m. There was no significant change in oxygen uptake at 16.1 km/h after the altitude training camp (mean \pm SE = 50.7 ± 0.5 and 49.3 ± 0.4 mL O_2 /min/kg before altitude, and 50.0 ± 0.5 mL/min/kg after altitude exposure; if anything, a small but not statistically significant increase in oxygen uptake was observed after altitude exposure ($P = 0.11$). When all three speeds were considered and economy calculated as the slope of the regression relating treadmill speed to oxygen uptake, economy was similarly

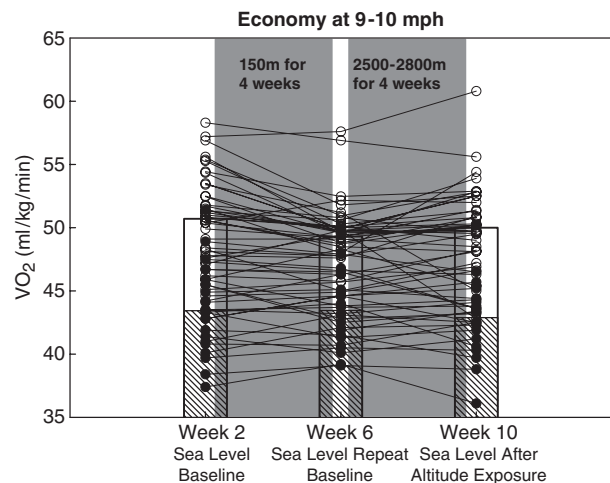


Fig. 1. Study A: individual whole-body VO_2 (mL/min/kg) during submaximal treadmill running at sea level before and after high-altitude exposure from studies A1 and A2 in 109 subjects. Open symbols were obtained during running at 16.1 km/h with mean data for this speed shown as open bars; filled symbols were obtained during running at 14.4 km/h with mean data for this speed shown as hatched bars.

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unchanged: 4.4 ± 0.0 and 4.4 ± 0.0 mL O₂/min/kg kph before altitude exposure, and 4.5 ± 0.0 mL O₂/min/kg kmp after exposure.

Study A2

For elite athletes, base pace oxygen uptake was unaffected by 4 weeks of living at 2500 m and training between 1250 and 2800 m: 51.2 ± 1.1 mL O₂/min/kg pre-altitude and 51.8 ± 0.6 mL O₂/min/kg post-altitude ($P = 0.39$). For race pace speeds, economy was similarly unaffected: 64.6 ± 1.2 vs 65.9 ± 1.1 mL O₂/min/kg).

Study A3

For the third group of highly trained collegiate athletes, submaximal oxygen uptake at 14.4 km/h was similarly unaffected by living at either 2500 or 2800 m, and training between 1250 and 2800 m: 43.4 ± 3.3 mL O₂/min/kg pre-altitude exposure vs 43.4 ± 2.8 mL O₂/min/kg after exposure ($P = 0.78$).

Thus, for the 109 highly competitive distance runners who participated in multiple different studies of moderate altitude exposure from 2500 to 2800 m over 6 years, in three different experienced laboratories, no changes in oxygen uptake were observed despite testing precision that should be sufficient to detect physiologically significant alterations in running economy.

Study B: SL residents investigated at SL and during acclimatization to 4100 m, and high-altitude natives investigated at 4100 m (Figs 2 and 3)

In the SL residents, no changes in whole-body or leg VO₂ were found during steady-state submaximal exercise, or during incremental exercise to maximum in any of the experimental settings. Compared with the SL residents, no difference in whole-body or leg VO₂ during submaximal exercise, or during incremental exercise to maximum was found in the high-altitude natives. Also, no changes were found with acute normoxic exercise in the high-altitude natives.

When whole-body economy was calculated as the slope of the regression relating exercise work load to pulmonary oxygen uptake, economy was similarly unchanged: 11.6 ± 0.1 , 11.2 ± 0.1 , 10.0 ± 0.1 , 11.1 ± 0.1 , 10.0 ± 0.1 , 9.9 ± 0.1 , 9.4 ± 0.1 , and 9.5 ± 0.1 mL O₂/min/W at SL, in AH, after 2 weeks of acclimatization with and without supplemental oxygen, after 8 weeks of acclimatization with and without supplemental oxygen before altitude exposure, and in high-altitude natives with and without supplemental oxygen, respectively.

When leg exercise economy was calculated as the slope of the regression relating exercise work load to

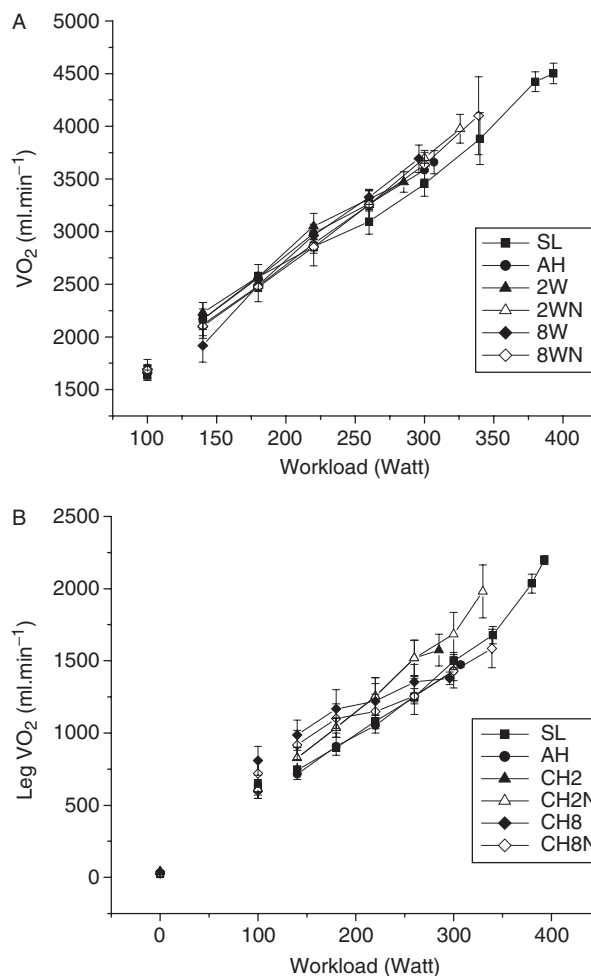


Fig. 2. (a, b). Study B: Whole-body VO₂ (mL/min) and leg VO₂ (mL/min) during cycle ergometer exercise in sea level (SL) resident at SL (■), acute hypoxia (AH, ●), after 2 weeks hypoxia in hypoxia (2 W, ▲), after 2 weeks in hypoxia with restored normoxia (2 W N, △), after 8 weeks hypoxia in hypoxia (8 W, ◆), after 8 weeks in hypoxia with restored normoxia (8 W N, ◇). Values are mean \pm SE.

leg oxygen uptake, economy was similarly unchanged: 4.4 ± 0.1 , 4.8 ± 0.1 , 5.3 ± 0.1 , 5.3 ± 0.1 , 4.5 ± 0.1 , 4.8 ± 0.1 , 4.9 ± 0.1 , and 4.8 ± 0.1 mL O₂/min/W at SL, in AH, after 2 weeks of acclimatization with and without supplemental oxygen, after 8 weeks of acclimatization with and without supplemental oxygen before altitude exposure, and in high-altitude natives with and without supplemental oxygen, respectively.

Study C: 1987, 1988, and 1991 pikes peak expeditions (Table 1)

For the 1987 experiments, whole-body and leg VO₂ (mL/min) were unchanged for all conditions. During the 1988 and 1991 expeditions, whole-body oxygen uptake (mL/kg) at 100-W cycle exercise was unaltered in all situations. However, during the same

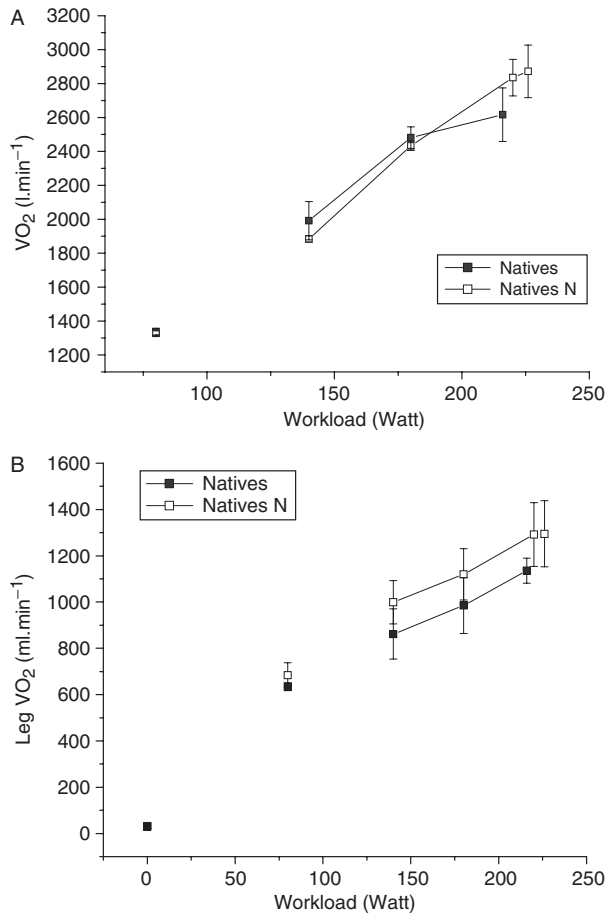


Fig. 3. (a, b). Study B: Whole-body VO_2 (mL/min) and leg VO_2 (mL/min) during cycle ergometer exercise in high-altitude natives in hypobaric hypoxia (■) and in acute hypobaric normoxia (□). Values are mean \pm SE.

Table 1. Study C: the Pike Peaks studies from 1987, 1988, and 1991

| | Sea level | 4300 m | |
|-------------------|---------------|---------------|---------------|
| | | 1 day | 21 days |
| Pikes peak 1987 | | | |
| Whole body, 150 W | 1208 \pm 36 | 1174 \pm 16 | 1146 \pm 19 |
| Leg, 150 W | 358 \pm 43 | 359 \pm 20 | 348 \pm 28 |
| Pikes peak 1988 | | | |
| Whole body, 100 W | 25.0 \pm 1 | 25.2 \pm 1 | 25.5 \pm 1 |
| Leg, 100 W | 605 \pm 43 | 473 \pm 25* | 532 \pm 26 |
| Pike peak 1991 | | | |
| Whole body, 100 W | 18.4 \pm 1 | 19.7 \pm 1 | 19.6 \pm 1 |
| Leg, 100 W | 441 \pm 23 | 368 \pm 21* | 384 \pm 14 |

Oxygen uptakes during 150 W cycle ergometer exercise for whole body (Whole body, 150 W) (mL/min) and leg (Leg, 150 W) (mL/min), and during 100 W cycle exercise for whole body (Whole body, 100 W) (mL/min/kg) and leg (Leg, 100 W) (mL/min). Blood flows were measured by the Bolus technique. * Compared with sea level.

exercise, leg VO_2 was decreased ($P < 0.05$) with 1 day of hypoxic exposure, but not after 21 days of acclimatization.

Table 2. Study D: workload (W) and pulmonary VO_2 (L/min) during submaximal cycle ergometer exercise and one-leg knee extensor exercise at sea level (6–9 months after return from high altitude), in acute hypoxia, and after 9 weeks of acclimatization to 5260 m altitude (chronic hypoxia)

| | Sea Level | Acute hypoxia | Chronic hypoxia |
|-----------------------------|-----------------|-----------------|-----------------|
| Cycle ergometer exercise | | | |
| Workload (W) | 116.4 \pm 0.3 | 116.4 \pm 0.3 | 116.4 \pm 0.3 |
| VO_2 (L/min) | 1.92 \pm 0.3 | 1.76 \pm 0.2* | 1.72 \pm 0.3* |
| One-legged kicking exercise | | | |
| Workload (W) | 30.6 \pm 0.5 | 30.6 \pm 0.5 | 30.6 \pm 0.5 |
| VO_2 (L/min) | 0.69 \pm 0.0 | 0.63 \pm 0.0* | 0.62 \pm 0.0* |

Values are mean \pm SE.

* $P < 0.05$ compared with sea level.

$P < 0.05$ compared with chronic hypoxia.

Study D: SL residents investigated at SL and with acute and 9 weeks of exposure to 5260 m (Table 2)

During continuous submaximal exercise at 116 \pm 0.3 W VO_2 was 1.92 \pm 0.3 L/min at SL and decreased ($P < 0.05$) to 1.76 \pm 0.2 L/min with acute hypoxic exposure. There was no further reduction in whole-body VO_2 after 9 weeks of acclimatization, the value being 1.72 \pm 0.3 L/min.

During continuous submaximal one-leg knee-extensor exercise at 31 \pm 0.6 W VO_2 was 0.69 \pm 0.0 L/min at SL and decreased ($P < 0.05$) to 0.63 \pm 0.0 L/min with acute hypoxic exposure. After acclimatization no further reductions were observed, the value being 0.62 \pm 0.0 L/min.

Discussion

The aim of the present study was to test rigorously whether chronic high-altitude exposure is accompanied by changes in muscle mechanical efficiency. The combined data of the large number of subjects studied in different laboratories show a remarkable consistency – no change in muscle mechanical efficiency with altitude acclimatization. In the two studies showing a decrease in VO_2 , the muscle mechanical efficiency was similar with acute and chronic hypoxic exposure, suggesting that hypoxia altered muscle metabolic substrate utilization rather than inducing an anatomical/physiological adaptation to high altitude.

Our finding of unchanged muscle mechanical efficiency during whole-body exercise at altitudes up to 4300 m is in agreement with the literature. Since first reported during the International Expedition to Chile in 1935 by Christensen (1937), this observation has been confirmed on numerous occasions (Pugh et al., 1964; Consolazio et al., 1966; Klausen et al., 1970; Maher et al., 1974; West et al., 1983; Bender et al., 1988; Svedenhag et al., 1991; Wolfel et al., 1991; Grassi et al., 1996; Young et al., 1996; Lundby

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& van Hall, 2002; Calbet et al., 2003). Of note is that submaximal VO_2 in these studies were all measured at altitude. In accordance, submaximal VO_2 has also been reported to remain unchanged if measured at SL after altitude acclimatization (Hansen et al., 1967; Klausen et al., 1970). The present investigation reports on the effect of altitude acclimatization on submaximal VO_2 measurements at SL, at altitude, and with acute induction of normoxia at altitude. In these studies, no reduction in submaximal VO_2 with altitude acclimatization was found.

However, recent publications measuring VO_2 after hypoxic exposure have challenged the general belief of an unaltered muscular efficiency (Green et al., 2000b; Gore et al., 2001; Saunders et al., 2004), and will be discussed separately:

(1) Green et al. (2000b) showed that in five untrained mountaineers following a 21-day mountaineering expedition to Mt. Denali (6189 m), with varying altitude exposure, that whole-body VO_2 during steady-state submaximal cycle ergometer exercise performed 3 days after return to SL was significantly reduced by approximately 0.2 L/min. Accordingly, mechanical efficiency increased from about 25% before the high-altitude sojourn, to values close to 30% after the expedition. This finding contradicts studies where subjects were exposed to 3800 m for 12 days (Klausen et al., 1970) or to 4300 m for 21 days (Hansen et al., 1967). In both studies, VO_2 was measured after return to SL and showed no differences compared with before altitude exposure.

The observed decrease in whole-body VO_2 after the climbing expedition to Mt. Denali was associated with a 13.8% downregulation in muscle Na^+/K^+ -ATPase in a subsequent publication (Green et al., 2000a). A decrease in Na^+/K^+ -ATPase has been hypothesized to allow a given amount of work to be performed at lower ATP costs, and hence at a lower VO_2 (Hochachka et al., 1991). Accordingly, the subjects from study D had a reported higher net release of K^+ during submaximal exercise after acclimatization to 5260 m. Net K^+ release depends on the balance between K^+ uptake and K^+ release, and the observed increase in K^+ could be a result of downregulated Na^+/K^+ -ATPase (Calbet et al., 2003). However, alterations of the Na^+/K^+ may also be altitude dependent, and no changes were observed in any of the three Na^+/K^+ pump subunits in muscle biopsies obtained after 2 and 8 weeks of high-altitude exposure to 4100 m in study B (Juel et al., 2003). Another explanation for the reduced submaximal VO_2 after the expedition to Denali could be related to the experimental design. Green and co-workers investigated their subjects at SL, whereas most others studied their subjects at high altitude. As the mechanical power of breathing for a given work rate is higher with hypoxic exposure (Cibella et al.,

1996), differences in submaximal VO_2 after acclimatization could be masked in hypoxia because of the extra energy required to move air to the lungs (Green et al., 2000b). However, as seen in Figs 2A, B and 3A, B where normoxia is induced acutely in chronic hypoxia, this does not seem to be the case. Finally, climbers on Denali are exposed to very harsh environmental conditions, and stimuli such as cold, marked changes in exercise habits, reduced availability, and different types of food could all conceivably have altered muscle structure and function under these extraordinary conditions. Extrapolation of these data to less severe high-altitude or hypoxic conditions should be carried out with caution.

In study D, we report on decreases in submaximal VO_2 during cycle and one-legged kicking exercise with acute and chronic hypoxic exposure to 5260 m as compared with SL. As the alterations were already present in the acute hypoxic situation, this response does not seem to be related to physiological adaptations associated with altitude acclimatization. The point that ΔVO_2 decreases as the altitude is increased has been observed by Wagner et al. (1986) in the mid-1980s, reporting decreases in submaximal VO_2 with increasing acute exposure to altitude as well as with increasing exercise intensity. The underlying regulating mechanism is unknown, but could be speculated to be related to increased carbohydrate utilization.

(2 and 3) Gore et al. (2001) studied the effects of spending 23 nights (9.5 h/day) at 3000 m on exercise performance at SL. In the six competitive cyclists, the investigated submaximal efficiency was improved from 18.9% to 19.7%. Considering the 3% margin of error typically associated with pulmonary gas exchange measurements, it seems unlikely that the reported 0.8% improvements in efficiency are all because of physiological changes. Another limitation in the study by Gore et al. (2001) is that the training was not supervised. Training alone might very well explain the rather small 0.8% increase in muscular efficiency (Franch et al., 1998), as we also observed in the SL training phase of the studies in group A1 (Fig. 1).

Recently, the same research group that conducted the experiments on which the Gore et al. (2001) article is based repeated the protocol except that this time training was controlled, and that the chosen exercise was running instead of cycling. Although no differences could be found in the slope between running speed and VO_2 (definition of economy), VO_2 was reported to be lower after the hypoxic exposure if the average VO_{2S} for all workload were used (Saunders et al., 2004). In contrast to these reports, however, is the publication of two articles from the same laboratory using similar experimental setups that were not able to detect differences in either mechanical efficiency or VO_2 (Telford et al., 1996; Clark et al.,

2004). When these small, inconsistent studies are viewed in the light of more than 100 subjects in study A, where reproducible results were observed, it seems reasonable to conclude that “live high–train low” does not consistently alter mechanical efficiency or submaximal VO_2 . Whether different combinations of duration/intensity of hypobaric or normobaric hypoxic living plus normoxic training could contribute to the divergent results reported in the literature is unknown.

Recently, studies applying repeated and very short-duration hypoxic exposure have been performed in order to evaluate its possible athletic effects. Katayama et al. (2003) reported that exposure to 432 mmHg (equivalent to 4500 m) for 90 min/three times a week/3 weeks reduced SL submaximal VO_2 during treadmill running. This is in contrast to exposure to 5500 m for the same time duration where no reductions in SL submaximal VO_2 were reported during bike ergometer exercise (Rodriguez et al., 2000). Recently, Katayama et al. (2004) also reported that intermittent exposure to 12.3% O_2 (about 4200 m) for 3 h daily for 14 days reduced submaximal running VO_2 . In contrast, our group has observed no differences in submaximal ergometer cycling VO_2 after 2 h daily exposure to 4100 m for 14 consecutive days in eight subjects (Lundby et al., 2005). This difference in results could be explained by the somewhat high values for submaximal economy in Katayama et al.'s (2004) subjects before the hypoxic exposure. For example, at 16.1 km/h before hypoxia exposure, the mean value for VO_2 was 54.4 mL/min/kg, with the majority (6/8) of the subjects above 52 mL/min/kg. In contrast, for all the subjects from experiment A reported in Fig. 1, before altitude exposure (after SL training), only 2/39 subjects had oxygen uptakes exceeding that level. Following hypoxia exposure, the hypoxia group had more normal and appropriate values for this work rate (52.5 mL/ O_2 /kg), which were identical to those of the control group, both before and after intervention. Thus, repeat testing, and/or SL training appeared to normalize excessively high oxygen uptakes in the group assigned to hypoxia exposure.

The above-mentioned studies showing reduced submaximal VO_2 after hypoxic exposure are supported by the classic paper by Hochachka et al. (1991), where high-altitude Andean natives were reported to have higher mechanical efficiencies than SL residents when compared at SL. However, the high-altitude subjects in that study were anemic and might therefore not serve as the best experimental group. Moreover, the controls were healthy Canadian athletes, with approximately 20 kg more body mass and an obviously different chronic nutritional state. Thus, it is not clear whether the differences reported between these groups are related to altitude

acclimatization, or rather socioeconomic or racial differences.

In contrast, in the present study, we did not find that the mechanical efficiency was any higher in high vs lowlanders, and also Favier et al. (1995) reported similar unchanged muscular efficiencies in high-altitude natives. Accordingly, in a recent publication by Wagner et al. (2002), no differences in whole-body VO_2 were found during graded cycling exercise to exhaustion between high-altitude natives and lowlanders acclimatized for 9 weeks to 5260 m. Also, natives to 2000 m altitude in Kenya are reported to have similar whole-body VO_2 s during graded exercise to maximum effort as compared with lowlanders acclimatized to this altitude for 14 days (Svedenhag et al., 1991). Thus, it seems that high-altitude natives are not different from lowlanders when it comes to mechanical efficiency.

Finally, further support to our contention that exercise economy remains unchanged after acclimatization to altitude can be found in the data from the Pikes Peak (Table 1). In these studies, not only was whole-body VO_2 unchanged with acclimatization but actual leg VO_2 remained unchanged as well both at rest and during fixed submaximal exercise. In some of these data, however, leg VO_2 were lower at altitude as compared with SL whereas this was never the case for whole-body VO_2 . The small reduction in leg VO_2 can be explained by acute changes in substrate utilization that are offset by a small increase in ventilatory and/or cardiac work so that total VO_2 is unchanged.

This would clearly suggest that the exercising muscles have not altered their metabolic efficiency. If muscle efficiency were improved, this would have been reflected in a lower leg VO_2 during exercise. This was not the case.

Limitations to our study

Another issue that needs to be addressed is whether or not this study adequately addresses the question of whether altitude exposure changes muscle mechanical efficiency. Numerous studies have shown that whole-body VO_2 after a primary fast rise, lasting 2–3 min, increases further by a slow component during intense, but not moderate, submaximal dynamic exercise. Although most of the slow component can be attributed to the exercising skeletal muscles (Poole et al., 1991), it is still debated whether fiber recruitment, muscle acidosis, muscle temperature, or even other factors are also involved (Whipp et al., 2002). In a situation with increases in VO_2 over time, potential changes in muscle efficiency are very difficult to measure. While the present studies C and D were performed below a work rate presumed necessary to induce the slow O_2 component, and thus unbiased by

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Table 3. Delta VO₂ (mL/min) between the last two 30 s recordings of the 2.5 min increments, i.e., the difference in VO₂ between recordings from 1.5 to 2 min and from 2 to 2.5 min

| Work rate | Lowlanders | | | | | | Aymaras | |
|-----------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| | SL | AH | 2W | 2WN | 8W | 8WN | Nat | NatN |
| 140 | 16 ± 0.3 (0.7%) | 15 ± 0.6 (0.7%) | 15 ± 0.2 (0.7%) | 9 ± 0.4 (0.4%) | 17 ± 0.6 (0.9%) | 15 ± 0.5 (0.7%) | 15 ± 0.6 (0.8%) | 18 ± 0.4 (1.0%) |
| 180 | 9 ± 0.3 (0.4%) | 5 ± 0.7 (0.2%) | 15 ± 0.5 (0.6%) | 18 ± 0.7 (0.7%) | 21 ± 0.7 (0.8%) | 19 ± 0.5 (0.8%) | 19 ± 0.5 (0.8%) | 24 ± 0.5 (1.0%) |
| 220 | 15 ± 0.5 (0.5%) | 14 ± 0.3 (0.5%) | 23 ± 0.6 (0.8%) | 14 ± 0.6 (0.5%) | 17 ± 0.6 (0.6%) | 22 ± 0.6 (0.7%) | | 17 ± 0.4 (0.6%) |
| 260 | 17 ± 0.2 (0.5%) | 19 ± 0.6 (0.6%) | 12 ± 0.2 (0.4%) | 16 ± 0.5 (0.5%) | 20 ± 0.4 (0.6%) | 16 ± 0.5 (0.5%) | | |
| 300 | 12 ± 0.4 (0.3%) | | | 17 ± 0.5 (0.5%) | | 16 ± 0.5 (0.4%) | | |
| 340 | 18 ± 0.4 (0.5%) | | | | | | | |

The % indicates the percentage of the “slowcomponent” in relation to the total O₂ uptake.

SL, sea level; AH, acute hypoxia.

this factor, studies A and B could be biased by a slow increase in VO₂. To test this, we randomly selected data from six subjects from the post-altitude testing in study A, and analyzed breath-by-breath data, which were collected simultaneously with the Douglas bags. We then compared the recordings from the bags filled during the first 30 s, and from the last 30 s of the exercise. The results, as expected, showed that there was absolutely no drift: first 30 s = 2930 ± 538 mL; last 30 s = 2939 ± 502 mL. The mean difference between the two time periods was thus only 9 mL/min and is absolute proof that there was no drift during the measurements in study A. Moreover, it should be emphasized that although 16.1 km/h may seem like a fast speed for an untrained, or even a fit, non-athletic individual, the subjects for experiment A were all trained runners, and this speed was typical of a base training pace that the subjects could maintain for hours. These oxygen uptakes were well below the ventilatory and lactate thresholds as reported in Levine and Stray-Gundersen (1997) and were even further below the ventilatory threshold for the elite athletes in study A2 (Stray-Gundersen, 2001). Thus, it is highly unlikely that drift during the measurements could be compromising the data. For study B, we performed similar analysis of our data, and Table 3 shows the difference in VO₂ between the last two 30-s

recordings for all workloads and all conditions. Also, for study B, there was no observed drift in VO₂ during any of the measures. Taken together, the above suggests that our measures are valid for the evaluation of muscle mechanical efficiency.

Perspectives

Submaximal VO₂ is unchanged at all times after exposure from moderate altitude (2500–3000 m) up to altitudes of 4300 m. At 5280 m, submaximal VO₂ is decreased as compared with SL both with acute and chronic exposure. Based on this stability, we propose that the decrease in VO₂ with acute, extreme hypoxia is unrelated to physiological/anatomical adaptations, but is rather a metabolic response associated with severe hypoxia.

Keywords: running, cycling, economy, efficiency, hypoxia, training.

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