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Pulmonary gas exchange at maximal exercise in Danish lowlanders during 8 wk of acclimatization to 4,100 m and in high-altitude Aymara natives

Carsten Lundby,[1] Jose A. L. Calbet,[1,2] Gerrit van Hall,[1] Bengt Saltin,[1] and Mikael Sander[1]

[1]*The Copenhagen Muscle Research Centre, 2100 Copenhagen Ø, Denmark; and* [2]*Department of Physical Education, University of Las Palmas de Gran Canaria, Grand Canary, Spain*

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Lundby, Carsten, Jose A. L. Calbet, Gerrit van Hall, Bengt Saltin, and Mikael Sander. Pulmonary gas exchange at maximal exercise in Danish lowlanders during 8 wk of acclimatization to 4,100 m and in high-altitude Aymara natives. *Am J Physiol Regul Integr Comp Physiol* 287: R1202–R1208, 2004. First published June 10, 2004; doi:10.1152/ajpregu.00725.2003.—We aimed to test effects of altitude acclimatization on pulmonary gas exchange at maximal exercise. Six lowlanders were studied at sea level, in acute hypoxia (AH), and after 2 and 8 wk of acclimatization to 4,100 m (2W and 8W) and compared with Aymara high-altitude natives residing at this altitude. As expected, alveolar P_{O_2} was reduced during AH but increased gradually during acclimatization (61 ± 0.7, 69 ± 0.9, and 72 ± 1.4 mmHg in AH, 2W, and 8W, respectively), reaching values significantly higher than in Aymaras (67 ± 0.6 mmHg). Arterial P_{O_2} (Pa_{O_2}) also decreased during exercise in AH but increased significantly with acclimatization (51 ± 1.1, 58 ± 1.7, and 62 ± 1.6 mmHg in AH, 2W, and 8W, respectively). Pa_{O_2} in lowlanders reached levels that were not different from those in high-altitude natives (66 ± 1.2 mmHg). Arterial O_2 saturation (Sa_{O_2}) decreased during maximum exercise compared with rest in AH and after 2W and 8W: 73.3 ± 1.4, 76.9 ± 1.7, and 79.3 ± 1.6%, respectively. After 8W, Sa_{O_2} in lowlanders was not significantly different from that in Aymaras (82.7 ± 1%). An improved pulmonary gas exchange with acclimatization was evidenced by a decreased ventilatory equivalent of O_2 after 8W: 59 ± 4, 58 ± 4, and 52 ± 4 l·min·l O_2^{-1}, respectively. The ventilatory equivalent of O_2 reached levels not different from that of Aymaras (51 ± 3 l·min·l O_2^{-1}). However, increases in exercise alveolar P_{O_2} and Pa_{O_2} with acclimatization had no net effect on alveolar-arterial P_{O_2} difference in lowlanders (10 ± 1.3, 11 ± 1.5, and 10 ± 2.1 mmHg in AH, 2W, and 8W, respectively), which remained significantly higher than in Aymaras (1 ± 1.4 mmHg). In conclusion, lowlanders substantially improve pulmonary gas exchange with acclimatization, but even acclimatization for 8 wk is insufficient to achieve levels reached by high-altitude natives.

chronic hypoxia; acute normoxia; ventilation

HIGH-ALTITUDE NATIVES from North America (8), Tibet (27), and South America (19, 25) have unique pulmonary gas transport abilities, maintaining low alveolar-arterial P_{O_2} difference (A-aP_{O_2}) at maximum exercise, thus preserving arterial P_{O_2} (Pa_{O_2}) and saturation (Sa_{O_2}). This confers a clear advantage to high-altitude natives compared with the lowlanders during exercise at altitude. Although pulmonary gas exchange in high-altitude natives has been the focus of several studies, only a few reports exist on pulmonary gas exchange during exercise in lowlanders acclimatized to high altitude. The classic study by Dempsey et al. (8) investigated lowlanders acclimatized to 3,100 m for 4, 21, and 45 days and compared these with first- to third-generation high-altitude residents. Despite the limited number of subjects analyzed (4 lowlanders), a comparatively low exercise A-aP_{O_2} was observed in the natives, whereas the lowlanders seemed to reduce their exercise A-aP_{O_2} as the altitude exposure was prolonged (8). More recently, Calbet et al. (5, 6) also found reduced exercise A-aP_{O_2} in seven lowlanders after chronic (9 wk) compared with acute (minutes) exposure to a very high altitude of 5,260 m. However, in the latter investigation, the time course of gas exchange improvement with acclimatization was not described. As part of the same field study, a similar group of lowlanders was compared with high-altitude natives residing at 3,700–4,100 m and acutely transported to 5,260 m. Despite the high-altitude, natives were not acclimatized to the higher altitude, but they still exhibited significantly lower A-aP_{O_2} during maximal exercise than the well-acclimatized lowlanders (25).

In the present study, three variables are considered indicators of pulmonary gas exchange: A-aP_{O_2}, ventilatory equivalent [ventilation ($\dot{V}_E$)/O_2 consumption ($\dot{V}_{O_2}$)], and Sa_{O_2}. The primary aim was twofold: The first was to test whether pulmonary gas exchange continues to improve in lowlanders during prolonged acclimatization to high altitude. In particular, we aimed to determine whether exercise pulmonary gas exchange continues to improve once hemoglobin (Hb) concentration has reached a steady state similar to that of the high-altitude natives. The second was to test whether prolonged acclimatization of lowlanders is accompanied by a pulmonary gas exchange comparable to that of high-altitude natives. To address these issues, Danish lowlanders were investigated during maximal exercise at sea level, in acute hypoxia, and after 2 and 8 wk of acclimatization to 4,100 m. They were compared with high-altitude Aymaras, born and residing at 4,100 m.

METHODS

Subjects. We studied six Danish male lowlanders, [26 (range 22–31) yr of age, 187 (range 175–191) cm, 82 (range 75–91) kg body wt] and eight Bolivian male high-altitude natives [31 (range 26–37) yr of age, 163 (range 157–170) cm, 63 (range 52–70) kg body wt]. The lowlanders were physical education students participating regularly in a variety of club sports and outdoor recreational activities. The high-altitude natives were also physically active in combat sports and soccer clubs. All Bolivians were born in and lifetime residents of La Paz/El Alto (3,700–4,100 m), and all were of Aymaran ancestry. Subjects received written and oral information in their native language and provided informed consent to the protocols. The protocol for the Danish subjects was approved by the Science Ethics Committee for

Address for reprint requests and other correspondence: C. Lundby, The Copenhagen Muscle Research Centre, Rigshospitalet, Sect. 7652, 9 Blegdamsvej, DK-2100 Copenhagen Ø, Denmark (E-mail: Carsten@cmrc.dk).

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Copenhagen and Frederiksberg (KF 11-050/01), and the protocol for the Danish and Bolivian subjects was approved by El Tribunal de Honor del Colegio Médico Departamental de La Paz and the Ministerio De Previsión Social y Salud Pública (La Paz, Bolivia).

Acclimatization of the lowlanders. The Danish subjects performed six incremental bicycle exercise tests on a cycle ergometer. At sea level (Copenhagen, Denmark), the subjects were tested twice, with 3–4 wk between the trials. In these tests, the subjects were breathing ambient air (sea level) or a hypoxic gas mixture [12.6% O_2 in N_2, acute hypoxia (AH)]. At ~1 mo after the last test at sea level, subjects traveled by plane to La Paz. Initially, they spent 2 nights in La Paz (~3,700 m) and then moved to El Alto (4,100 m, ~470 mmHg) for the remaining 8 wk of the study. The subjects lived together in an apartment and prepared their own meals. They maintained their habitual Danish diet, which is rich in cereal, pasta, and rice, and occasionally visited fast-food restaurants. They remained physically active by running, weightlifting, and playing football and basketball during their stay in El Alto. At 3–4 wk of acclimatization, the subjects had short excursions from El Alto but were not allowed to descend below 3,700 m. The first testing period at altitude was 11–17 days after arrival at La Paz. The incremental bicycle exercise test was carried out first while the subjects breathed ambient air (2W) and then ~2 h later while the subjects breathed a high-O_2 gas mixture eliciting sea-level conditions: 38% O_2 in N_2 (2WN). The second test period at altitude was 52–60 days after arrival at La Paz and was conducted exactly as described for the first tests (8W and 8WN).

Procedures and measurements. The procedures for the lowlanders at sea level and at altitude and for the high-altitude natives were similar. The subjects had a light breakfast and reported to the laboratory at 8 AM. Under local anesthesia (lidocaine, 20 mg/ml), catheters were placed in a femoral artery (20 gauge, 12 cm; Arrow) and vein (18 gauge; Radiopack TFE, Cook, Bjaerverskov, Denmark) for blood sampling. Intra-arterial blood pressure was measured at the level of the heart and at the inguinal ligament by adjustment of the position of the pressure transducer (Baxter, Unterschleissheim, Germany), which was interfaced with a blood pressure amplifier (BPamp, ADinstruments, Sydney, Australia). The venous catheter was used to measure leg blood flow by the constant-infusion thermodilution technique described in detail previously (1). Briefly, a thermistor (model 94-030-2.5F TD probe, Edslab, Baxter, Irvine, CA) was inserted to measure femoral blood temperature, while infusate temperature was determined with a flow-through chamber thermistor (model 93-505, Edslab, Baxter) connected to the venous catheter. The signal from both thermistors was conditioned and amplified by a custom-built interface (FBJ Industries). During catheterization and the remainder of the study, we continuously monitored the electrocardiogram (BIO amp, ADinstruments) and arterial blood pressure. We used an analog-to-digital converter and data acquisition software (Powerlab/8SP and Chart 4, ADinstruments) to display and store the electrocardiogram, blood pressure, and temperature data on a portable computer (Dell). After catheterization, the subjects remained supine for ≥30 min. Subjects were then seated on a bicycle ergometer (model 824E, Monark, Varberg, Sweden) and fitted with a mouthpiece and nose clip to enable measurements of ventilation, $\dot{V}_{O_2}$, and CO_2 production from expired gas (S-3A/I O_2 analyzer, Ametek; LB-2, Beckman; and VRDC/HC-1, Parvo Medics). Blood was sampled anaerobically in heparinized syringes and immediately analyzed for Hb and Sa_{O_2} (OSM3 hemoximeter, Radiometer) and blood pH, CO_2 tension (Pa_{CO_2}), and Pa_{O_2} (model ABL5, Radiometer). Hematocrit (Hct) was determined by centrifugation of capillary tubes.

To address other scientific questions, additional blood samples and muscle biopsies from the vastus lateralis were obtained, under local anesthesia (lidocaine, 20 mg/ml), at rest and after warm-up and exhaustive exercise. Thus the data reported in this study from Danish and Bolivian subjects are only part of the data obtained. Metabolic, biopsy, and leg blood flow measurements unrelated to the present study are reported elsewhere (13, 24).

Protocol. Resting measurements started 10 min after placement of the mouthpiece, while the subjects were seated on the cycle ergometer, and at this time, the resting blood samples were obtained. Exercise started with 15 min of warm-up at 100 W for the lowlanders and 80 W for the high-altitude natives. After warm-up, the workload was increased by 40 W every 2.5 min until exhaustion for the lowlanders. The first increment for the high-altitude natives after the warm-up was 20 W followed by increments of 40 W until exhaustion. During the last minute of each workload, blood flow was measured, blood was sampled, and blood flow was measured again. At altitude, 2 h after the first incremental exercise, the protocol was repeated while the subjects breathed the O_2-supplemented gas mixture [inspiratory O_2 fraction (FI_{O_2}) = 0.38].

All subjects were familiar with maximal exercise testing on cycle ergometers from participation in previous experiments and were familiarized with the actual cycle ergometer used during pretrials. All studies were performed with vigorous verbal encouragement as the subjects approached exhaustion.

Calculations. The measured pH, P_{O_2}, P_{CO_2}, and Sa_{O_2} were corrected for temperature according to Severinghaus (20) using the blood temperature measured in the femoral vein. Plasma bicarbonate was calculated according to Siggaard-Andersen (21), and blood base deficit was calculated on the basis of the van Slyke equation of Siggaard-Andersen and corrected for hypercarbia and O_2 desaturation according to Schlichtig (18). The standard P_{50}, defined as the P_{O_2} at which Hb is saturated by 50% when the O_2-Hb equilibration curve is determined at 37°C, pH 7.40, and 40 mmHg P_{CO_2}, was calculated from the whole set of arterial and venous gases obtained in each experiment.

Statistical analysis. Values are means ± SE. For all data, the assumption of normal distribution was verified using the Shapiro-Wilk test, and the assumption of equal variances was verified using the *F*-test. Differences between conditions in the Danish lowlanders were analyzed by two-way ANOVA for repeated measures followed by Tukey's post hoc test. Student's *t*-tests for unpaired data were used to detect differences between high-altitude natives and Danish lowlanders. Statistical significance was set at $P < 0.05$. Bonferroni's correction for significance level was used as appropriate.

RESULTS

Resting arterial blood gases. In lowlanders, Hct and Hb concentration increased markedly during the first 2 wk of acclimatization and did not increase further over the subsequent 6 wk at altitude (Table 1). Hb and Hct in the high-

Table 1. *Resting arterial blood gas values at sea level, in acute hypoxia, and after 2 and 8 wk of acclimatization in Danish lowlanders and high-altitude natives*

	Lowlanders (n = 6)				Aymaras (n = 8)
	SL	AH	2W	8W	
Hb, g/l	139±2	131±4	163±3*	159±3*	167±4
Hct, %	42.4±0.7	41.4±0.9	49.2±1.0*	47.6±1.0*	50.2±1.2
Pa_{O_2}, mmHg	93±2.1	45±0.9*	51±1.3*	54±1.2*	57±1.0
Sa_{O_2}, %	98.4±0.1	87.9±0.6*	89.7±0.8*	90.9±0.4*	87.3±0.7†
Ca_{O_2}, ml/l	191±3	160±6*	204±6	201±4	203±6
Pa_{CO_2}, mmHg	39±1.3	36±0.5	26±0.4*	25±0.4*	27±1.0
pH	7.41±0.01	7.44±0.01	7.46±0.01*	7.47±0.01*	7.44±0.01†

Values are means ± SE; n, number of subjects. SL, sea level; AH, acute hypoxia; 2W and 8W, after 2 and 8 wk of acclimatization; Hb, hemoglobin; Hct, hemotocrit; Pa_{O_2}, arterial P_{O_2}; Sa_{O_2}, arterial O_2 saturation; Ca_{O_2}, arterial O_2 content; Pa_{CO_2}, arterial P_{CO_2}. *$P < 0.05$ vs. SL. †$P < 0.05$ vs. 8W.

altitude natives were not significantly different from those observed in the lowlanders after 2 and 8 wk of acclimatization. As expected, the hematological adjustments to altitude had occurred within the first 2 wk.

Maximal $\dot{V}O_2$ and power output. In lowlanders at sea level, acute hypoxia caused maximal $\dot{V}O_2$ ($\dot{V}O_{2\,max}$) and power output (W_{max}) to decrease by 20 and 22%, respectively (Table 2). At high altitude, $\dot{V}O_{2\,max}$ and W_{max} had decreased further after 2 wk but recovered after 8 wk. When $\dot{V}O_{2\,max}$ and W_{max} were expressed relative to body weight, no significant differences were found between acute hypoxia and the high-altitude trials [$\dot{V}O_{2\,max} = 45 \pm 1$, 44 ± 1, and 47 ± 1 ml·min^{-1}·kg^{-1} in AH, 2W, and 8W, respectively, P = not significant (NS); $W_{max} = 3.7 \pm 0.2$, 3.6 ± 0.2, and 3.8 ± 0.1 W/kg in AH, 2W, and 8W, respectively, P = NS]. Acutely restoring arterial saturation to sea level values at high altitude ($F_{I_{O_2}} = 0.38$) enhanced $\dot{V}O_{2\,max}$ and W_{max} in the lowlanders by 13 and 15% at 2 wk and 8 wk, respectively, and by 7% in the high-altitude natives.

$\dot{V}O_{2\,max}$ and W_{max} were lower in the high-altitude natives than in the lowlanders. When expressed relative to body weight, $\dot{V}O_{2\,max}$ and W_{max} were similar in lowlanders and high-altitude natives (43 ± 2 ml·min^{-1}·kg^{-1} and 3.5 ± 0.1 W/kg, respectively, P = NS compared with lowlanders during acute hypoxia and ambient air breathing at high altitude). Increasing O_2 supply to the lungs ($F_{I_{O_2}} = 0.38$) significantly increased $\dot{V}O_{2\,max}$ and W_{max}, even in high-altitude natives.

Pulmonary gas exchange and arterial oxygenation. In lowlanders at sea level, acute hypoxia reduced alveolar P_{O_2} ($P_{A_{O_2}}$), Pa_{O_2}, and Sa_{O_2} during maximal exercise (Table 2, Fig. 1). The decrease in Sa_{O_2} during exercise compared with rest was ~15%. This deoxygenation occurred despite a 12% increase in $\dot{V}E$. There was a 40% increase in $\dot{V}E/\dot{V}O_{2\,max}$, accompanied by a nonsignificant increase in A-aP_{O_2}.

In lowlanders at high altitude, 2 wk of acclimatization caused an increase of $P_{A_{O_2}}$ during maximal exercise (by 8 mmHg, $P < 0.05$) and a trend toward improved Pa_{O_2} compared with acute hypoxia. The decrease in Sa_{O_2} during exercise compared with rest remained at 13%, which was not significantly different from acute hypoxia. This recovery could be caused mainly by hematological adjustments. Interestingly, after 8 wk of acclimatization, although there was no further increase in Hb and Hct, $P_{A_{O_2}}$, Pa_{O_2}, and Sa_{O_2} continued to improve significantly compared with 2 wk. After 8 wk at high altitude, the decrease in Sa_{O_2} during exercise compared with rest was significantly reduced compared with acute hypoxia but remained at 11%. This improved oxygenation was accomplished despite significant 6 and 10% lower $\dot{V}E$ after 2 and 8 wk, respectively. $\dot{V}E/\dot{V}O_{2\,max}$ was significantly decreased only after 8 wk. There was no significant change in A-aP_{O_2} in the lowlanders at high altitude. Increasing O_2 supply ($F_{I_{O_2}} = 0.38$) prevented desaturation during exercise. At $F_{I_{O_2}} = 0.38$, Pa_{O_2} was higher than at sea level. Despite supranormal Pa_{O_2}, $\dot{V}E$ and A-aP_{O_2} did not change significantly, whereas $\dot{V}E/\dot{V}O_{2\,max}$ improved significantly after 2 wk but not after 8 wk.

Maximal exercise caused less deoxygenation in the high-altitude natives than in the lowlanders. $P_{A_{O_2}}$ and Pa_{O_2} were not significantly different at maximal exercise in high-altitude natives compared with the 8-wk values in the lowlanders. However, in the high-altitude natives, the decrease in Sa_{O_2} during exercise compared with rest was <5%, which was significantly lower than the desaturation observed in the lowlanders breathing hypoxic air. Because the lowlanders had somewhat lower resting values, the absolute end-exercise Sa_{O_2} in high-altitude natives was not different from the 8-wk value in the lowlanders. The lower maximal $\dot{V}E$ in the high-altitude natives was due to their smaller frames. $\dot{V}E/\dot{V}O_{2\,max}$ in high-altitude natives was not significantly different from that in lowlanders after 8 wk. However, A-aP_{O_2} was remarkably low (1 mmHg) in all high-altitude natives, even during maximal exercise, and the average was significantly lower than the values for lowlanders in any hypoxic trial. As previously mentioned, W_{max} per kilogram of body weight was similar in the high-altitude natives and the lowlanders. When expressed as $W_{max}/\dot{V}E$, the values were also similar in the two groups during the high-altitude trials (1.4 ± 0.06, 1.6 ± 0.06, and 1.6 ± 0.1 W·min·l^{-1} at 2 and 8 wk and in high-altitude natives, respectively, P = NS).

P_{CO_2}, pH, and Hb O_2 affinity. In lowlanders at sea level, Pa_{CO_2} was reduced during hypoxia at rest and during exercise (Tables 1 and 2). Arterial pH was higher during hypoxia than

Table 2. *Data obtained at maximum exercise in Danish lowlanders at sea level, in acute hypoxia, and after 2 and 8 wk of acclimatization and in high-altitude Aymaras with increased O_2 supply ($F_{I_{O_2}} = 0.38$) to achieve normoxemia in lowlanders and high-altitude natives*

	Lowlanders (n = 6)						Aymaras (n = 8)	
	SL	AH	2W	2WN	8W	8WN	Nat	NatN
$\dot{V}O_2$, l/min^{-1}	4.5±0.1	3.7±0.1^{f}	3.5±0.1^{bf}	4.0±0.1^{ef}	3.7±0.1^{f}	4.2±0.2^{ef}	2.6±0.2^{a}	2.9±0.2^{ae}
W_{max}, W	394±12	302±9^{f}	285±8^{f}	330±10^{ef}	296±5^{f}	339±12^{ef}	217±6^{a}	227±12^{ae}
$\dot{V}E$, l/min^{-1}	193±5	215±8^{f}	201±4	194±6	192±3	186±5	137±4^{a}	135±4^{a}
$\dot{V}E/\dot{V}O_2$, l/l O_2	43±5	59±4^{f}	58±4^{f}	49±2	52±4	46±3	51±3	51±2
$P_{A_{O_2}}$, mmHg	113±0.8	61±0.7^{cf}	69±0.9^{bf}	140±0.9^{ef}	72±1.4^{bf}	144±1.0^{ef}	67±0.6^{a}	144±0.7^{e}
PaO_2, mmHg	109±2.9	51±1.1^{cf}	58±1.7^{cf}	132±2.1^{e}	62±1.6^{bf}	140±1.7^{e}	66±1.2^{f}	141±2.6^{e}
A-aP_{O_2}, mmHg	4±3.5	10±1.3^{c}	11±1.5^{c}	9±2.4^{c}	10±2.1^{ce}	3±1.8	1±1.4	2±2.7
Sa_{O_2}, %	96±1.1	73±1.4^{cf}	77±1.7^{cf}	96±0.6^{e}	79±1.6^{df}	96±0.4^{e}	83±1.0	97±0.1^{e}
Pa_{CO_2}, mmHg	34±0.7	29±0.5^{cf}	24±0.9^{bf}	27±1.0^{f}	20±1.3^{bf}	26±0.7^{f}	27±0.8^{a}	28±1.3
pH	7.21±0.02	7.27±0.03	7.29±0.02	7.28±0.02	7.27±0.02	7.24±0.02	7.30±0.01	7.31±0.01
T_{bl}, °C	39.3±0.2	38.4±0.1	38.3±0.1	38.8±0.2	38.6±0.1	39.0±0.2	38.6±0.1	38.7±0.2

Values are means ± SE. Blood gas data are corrected to femoral vein temperatures. Nat, Aymaras; 2 WN, 8WN, and NatN, increased O_2 supply (inspiratory O_2 fraction = 0.38) to achieve normoxemia; $\dot{V}O_2$, O_2 uptake; $\dot{V}E$, pulmonary ventilation; $\dot{V}E/\dot{V}O_2$, ventilatory equivalent; W_{max}, power output; $P_{A_{O_2}}$ alveolar P_{O_2}; Pa_{O_2}, arterial P_{O_2}; A-aP_{O_2}, alveolar-arterial P_{O_2} difference; Sa_{O_2}, arterial O_2 saturation; Pa_{CO_2}, arterial P_{CO_2}; T_{bl}, femoral vein blood temperature; $^{a}P < 0.05$ vs. 2W. $^{b}P < 0.05$ vs. AH. $^{c}P < 0.05$ vs. Nat. $^{d}P < 0.05$ vs. 2W. $^{e}P < 0.05$, normoxia vs. hypoxia in 2W, 8W, and Nat. $^{f}P < 0.05$ vs. SL.

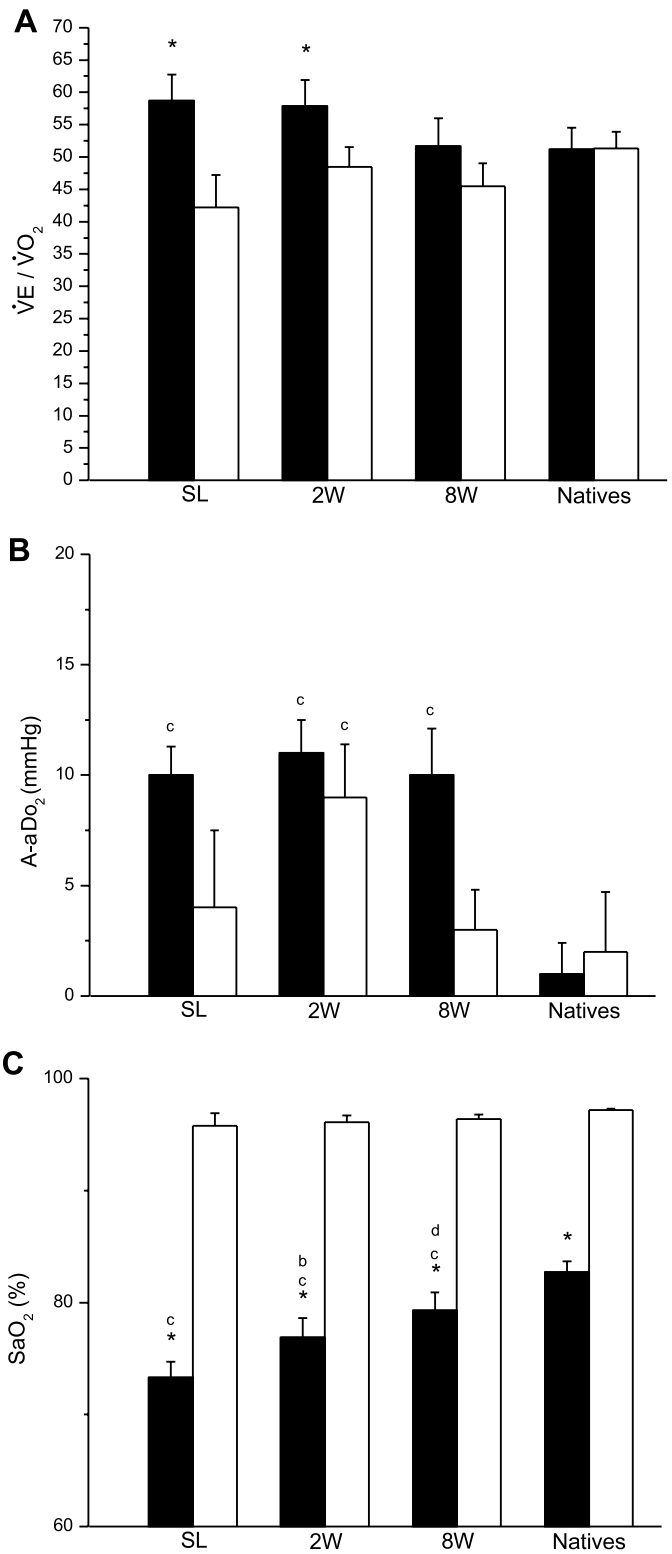

Fig. 1. Data obtained at maximum exercise in Danish lowlanders ($n = 6$) at sea level (SL) and after 2 wk (2W) and 8 wk (8W) of acclimatization and in high-altitude Aymaras (natives). Open bars, normoxemia; solid bars, hypoxemia. Blood gas data are corrected to femoral vein temperatures. *A*: ventilatory equivalent [ventilation ($\dot{V}_E$)/O_2 uptake ($\dot{V}O_2$), l/l O_2]. *B*: alveolar-arterial P_{O_2} difference (A-aP_{O_2}). *C*: arterial O_2 saturation (Sa_{O_2}). Values are means ± SE. *$P < 0.05$ vs. SL; [b]$P < 0.05$ vs. acute hypoxia; [c]$P < 0.05$ vs. natives; [d]$P < 0.05$ vs. 2W.

normoxia at rest and at the end of exercise. P_{50} was unchanged during acute hypoxia compared with sea level (26.0 ± 0.3 and 26.2 ± 0.3 mmHg at sea level and acute hypoxia, respectively). As expected, P_{50} increased slightly (27.8 ± 0.4 and 27.9 ± 0.4 mmHg after 2 and 8 wk, respectively, both $P < 0.05$ compared with sea level). O_2 supplementation caused minor increases in Pa_{CO_2} during exercise but no change in pH.

In high-altitude natives, resting Pa_{CO_2}, pH, and P_{50} were not different from the lowlanders after 2 and 8 wk of acclimatization (P_{50} = 28.3 ± 0.6 mmHg in high-altitude natives, P = NS). During exercise, the high-altitude natives did not decrease Pa_{CO_2} compared with rest and decreased pH somewhat less than the lowlanders.

DISCUSSION

The primary findings of the present study are as follows: *1*) Pulmonary gas exchange as determined by A-aP_{O_2} and $\dot{V}_E/\dot{V}O_2$ during maximal exercise is not improved during the initial 2 wk of acclimatization to 4,100 m. At this time, the minor increase in arterial saturation may be related to hematological adjustments affecting Hb O_2 affinity. *2*) In contrast, pulmonary gas exchange is improved after 8 wk of acclimatization. Thus, despite no further hematological adjustments at this time, $\dot{V}_E/\dot{V}O_2$ decrease and Sa_{O_2} increase during maximal exercise compared with 2 wk of acclimatization and reach values close to those of high-altitude natives. However, maximal exercise desaturation and A-aP_{O_2} remain significantly higher in lowlanders than in high-altitude Aymara natives. *3*) When supplemental O_2 is given at altitude to reproduce inspired P_{O_2} at sea level, lowlanders and high-altitude natives improve $\dot{V}O_{2\,max}$ by 7–13%.

The focus of the present study was to *1*) determine whether pulmonary gas exchange continues to improve during the course of high-altitude acclimatization in lowlanders and *2*) to compare pulmonary gas exchange in high-altitude natives and well-acclimatized lowlanders.

Pulmonary gas exchange during the course of acclimatization in lowlanders. Dempsey et al. (8) were among the first to study the time course of pulmonary gas exchange acclimatization to high altitude. They reported that arterial saturation and A-aP_{O_2} improved during the first 3 wk at 3,100 m but then surprisingly regressed to sea-level values during further exposure to altitude. The present study confirms an initial improvement in pulmonary gas exchange, because arterial saturation at maximal exercise was improved after 2 wk at 4,100 m. However, in contrast to the previous study, we have demonstrated a further improvement over time. Although our calculations of A-aP_{O_2} showed no improvement in this parameter over time, Sa_{O_2} and $\dot{V}_E/\dot{V}O_2$ were significantly improved between 2 and 8 wk of exposure to altitude. This improvement in pulmonary $\dot{V}O_2$ occurred without further increase in Hb concentration between 2 and 8 wk.

We suggest the following possible underlying mechanisms for the improved overall pulmonary gas exchange in the present study. *1*) The improved gas exchange is related to the increased $P_{A_{O_2}}$ (with an unchanged A-aP_{O_2}). This could be accomplished by improved alveolar ventilation. Indeed, the 4-mmHg lower Pa_{CO_2} at maximal exercise after 8 wk than at 2 wk may be an indication of improved alveolar ventilation. *2*) The increase in $P_{A_{O_2}}$ could be overestimated; i.e., the error of

the calculated $P_{A_{O_2}}$ does not remain constant under the different conditions. If this is so, the improved gas exchange may be related to an actual improvement in A-aP_{O_2} (and minor changes in alveolar ventilation). Indeed, an unchanged total ventilation does not imply large changes in alveolar ventilation. These two mechanisms are not mutually exclusive.

The circulatory adjustments of the lung may include increased capillarization. Indeed, a recent study reported increased angiogenesis and capillary density in the lungs of rats subjected to 2 wk of chronic hypoxia equivalent to 5,500 m (12). In contrast, increased maximal cardiac output, i.e., more blood and Hb moving through the pulmonary capillaries, is less likely, because recent invasive measurements showed that cardiac output during maximal exercise was reduced to the same extent during acute exposure and after 9 wk of acclimatization to severe hypoxia of high altitude (5, 6).

Pulmonary gas exchange in high-altitude natives vs. acclimatizing lowlanders. At maximal exercise, the mean A-aP_{O_2} for the high-altitude natives was 2 mmHg. This is considerably lower than 11–12 mmHg observed in the lowlanders after 2 and 8 wk of acclimatization and also lower than ~14 mmHg reported in high-altitude residents (1st–3rd generation) at 3,100 m (7) and in native Tibetans at 3,658 m (27). However, our data approximate the A-aP_{O_2} of ~5 mmHg in Aymara Indians taken acutely from 4,100 to 5,260 m (25). The explanation for the lower A-aP_{O_2} in the Bolivian Aymara natives in the previous and the present study compared with high-altitude residents of Colorado and Tibet may be largely related to differences in temperature correction of $P_{a_{O_2}}$. In our Bolivian studies, we used femoral venous temperature, which is ~2°C higher than the 37°C used in Colorado and Tibetan residents. A-aP_{O_2} would have been 10 ± 2 mmHg in the Aymara natives if we had used 37°C in the present study. The use of femoral venous temperature could represent an overcorrection of $P_{a_{O_2}}$. The femoral venous blood represents ~80% of venous return during maximal ergometer exercise. The remaining 20% is likely to have a lower temperature (e.g., from skin circulation). Furthermore, in the lungs, a significant alveolar-capillary temperature exchange is likely to occur, especially during high levels of ventilation. Therefore, the femoral artery blood temperature is likely to be somewhat lower than the femoral venous temperature. However, previous direct comparisons between femoral venous and esophageal core temperatures during maximal bicycle exercise revealed a variation of only 0.1°C (10). Thus the difference in temperatures between site of measurement (vein) and sampling (artery) must be minor.

Regardless of the temperature correction, we found a large difference in A-aP_{O_2} between lowlanders and Aymara high-altitude natives. The 1-mmHg A-aP_{O_2} in Aymara natives could be caused by enhanced diffusion. Indeed, Wagner et al. (25) estimated that Aymaras have a 173% higher diffusion capacity than the lowlanders. This value is similar to the diffusion capacity measured by carbon monoxide dilution in Quechua Indians of the Chilean altiplano (19).

A higher level of pulmonary ventilation-perfusion mismatch in the lowlanders than in the high-altitude natives is a potential alternative explanation for the difference in A-aP_{O_2}. A previous study in conscious dogs concluded that ventilation-perfusion mismatch actually decreased, whereas diffusion limitation increased, during exercise at acute exposure to simulated high altitude (~6,000 m) compared with sea level (22). However, in humans at a more moderate altitude (3,800 m), augmented pulmonary arterial pressure and ventilation-perfusion mismatch (shunting) have been demonstrated in lowlanders during exercise within the first days of acclimatization (15). It is possible that acclimatizing lowlanders during exercise have higher pulmonary arterial pressures than high-altitude natives. Indeed, one study provides evidence that high-altitude natives (~3,600 m) of Tibet have near-normal pulmonary arterial pressures at rest and exhibit very little increase during exercise (11). However, in another study, high-altitude natives of La Paz (~3,800 m) have significant increases in pulmonary arterial pressure during exercise (13). In the latter study, the magnitude of pulmonary arterial pressure during rest and exercise (29 ± 6 and 43 ± 13 mmHg) were not very different from that in lowlanders exposed acutely to a similar altitude (15 ± 3 and 39 ± 1 mmHg) (26). In the present study, we have not measured or estimated pulmonary arterial pressure. Even if we assume that pulmonary pressures were similar in lowlanders and high-altitude natives, we cannot exclude the possibility of a differential functional significance of the increased pulmonary pressure during maximal exercise in the two groups; i.e., shunting may become more pronounced in lowlanders at high altitude. During supplemental O_2 at high altitude, pulmonary arterial pressures during rest and exercise are significantly lowered (14). In the present study, supplemental O_2 decreased A-aP_{O_2} by 3 and 7 mmHg in the lowlanders after 2 and 8 wk, respectively. This improvement reached significance only after 8 wk, and at this time there was no longer a significant difference between the lowlanders and the high-altitude natives. Thus a more pronounced ventilation-perfusion mismatch caused by increased maximal exercise pulmonary pressures during ambient air breathing could be partly responsible for the higher A-aP_{O_2} in lowlanders than in high-altitude natives.

It is an interesting contrast to the persistent difference in A-aP_{O_2} that $\dot{V}_E/\dot{V}_{O_2}$ improved during acclimatization of the lowlanders to a level not distinguishable from that of the high-altitude natives. Thus, despite a higher A-aP_{O_2}, the ventilation required for a given $\dot{V}_{O_2}$ is similar in well-acclimatized lowlanders and Aymara natives. In a previously published study (3), high-altitude natives (n = 21) of La Paz studied at 3,600 m had significantly lower $\dot{V}_E/\dot{V}_{O_2}$ than European/North American residents at this altitude (minimum duration of acclimatization was 2 mo, n = 24). However, the difference was only 15%, which is lower than the 40% difference observed between normoxia and acute hypoxia at sea level. It is possible that we may have missed a difference in $\dot{V}_E/\dot{V}_{O_2}$ between the groups because of the small sample sizes.

Arterial saturation during maximal exercise was not significantly different in high-altitude natives (83%) and lowlanders (79%) acclimatized for 8 wk. However, although the exercise-induced desaturation improved during acclimatization, the degree of exercise-induced desaturation remained significantly higher, even after 8 wk, in lowlanders (12%) than in high-altitude natives (4%).

Genetic and developmental factors. Improved lung diffusion or decreased ventilation-perfusion mismatch during maximal exercise could be the result of genetic (phenotype selection over millennia) and/or developmental adaptation (i.e., structural organization of the lung during growth). This issue is addressed in studies comparing high-altitude inhabitants genet-

ically descending from high-altitude or lowland populations. In a relatively large study, Tibetans born and raised at high altitude (Tibetan descent) had higher near-maximal exercise Sa_{O_2} than Chinese residents at the same altitude (Chinese descent) who were moved there in adulthood and had lived at high altitude for >1 yr (27). A previously mentioned study (3) from La Paz finding a more efficient $\dot{V}_E/\dot{V}_{O_2}$ in residents of Aymara/Quechua than in individuals of European/North American descent also showed that the difference disappeared when the subjects of Indian descent were compared with two groups of European/North American immigrants born or arriving in La Paz before 18 yr of age (3). A potentially confounding factor would be non-Indian gene admixture in the high-altitude natives. In many studies, including the present, the degree of admixture is unknown.

In a recent study (4), $\dot{V}_{O_2\,max}$ at altitude was determined in 30 young Peruvian men exhibiting various degrees of genetic admixture between native Quechua Indian and Spanish ancestry. All subjects were born and raised at sea level and had matched high-altitude ancestry. In subgroup analyses, a positive correlation was found between the decrement of $\dot{V}_{O_2\,max}$ in high altitude and increasing Spanish gene admixture. However, when the subgroups with low (average ~1%) and high (average 18%) Spanish gene admixture were compared, the decrement in $\dot{V}_{O_2\,max}$ at altitude compared with sea level was 20 and 19%, respectively. Thus, although the study provides an important proof of the concept that genetic admixture is of relevance to performance in high altitude, the differences observed in $\dot{V}_{O_2}$ in South American Indian populations with some variation in genetic admixture seem to be minor. In a larger study of 381 Aymara natives residing at 3,900–4,000 m not far from La Paz, the hypothesis that genetic factors contributed to the variance of resting O_2 saturation was rejected on the basis of covariance analyses (2). In the most thorough analysis to date using the method of Szathmary and Reed (23) and based on 10–12 genetic systems and 40,040–52,446 alleles, the average value for the non-Indian admixture in Aymara Indians in the 1970s was actually 5% (16, 17). With a relatively minor effect of an even larger admixture in a subgroup of Quechua (4), it is unlikely that non-Indian admixture caused severe underestimation of the differences between the Aymaras and lowlanders of the present study.

Taken together, it remains likely that genetic factors and childhood development contribute to the low $A\text{-}aP_{O_2}$ and decreased exercise-induced desaturation, which have been demonstrated in the Aymaras included in the present study.

Effect of supplemental O_2 in high-altitude natives. In the present study, the Aymaras' $\dot{V}_{O_2\,max}$ increased by 7% with O_2 supplementation, which is in agreement with the 8% reported in a sample from the same population by Favier et al. (9). Compared with the Aymaras, O_2 supplementation increased the lowlanders' $\dot{V}_{O_2\,max}$ slightly more: by 10% at 2 wk and 13% at 8 wk. The greater improvement is likely because normoxia increases arterial saturation more in the Danish subjects than in the high-altitude natives. The present study and the study by Favier et al. (9) are at odds with the recent publication by Wagner et al. (25), where no improvements in exercise capacity was found when supplemental O_2 was given to a similar group of high-altitude natives. Two factors could explain the differences: *1*) The subjects studied by Wagner et al. were investigated during acute exposure to 5,260 m, which was considerably higher than their altitude of residence (3,600–4,100 m). *2*) O_2 supplementation was administered immediately before exhaustion during an exercise test performed during ambient air breathing.

The level of improvement in $\dot{V}_{O_2}$ and power output observed in the Danish subjects presents two questions: *1*) Why does O_2 supplementation fail to normalize $\dot{V}_{O_2}$ and power output to sea level values, despite supranormal arterial O_2 content (Ca_{O_2})? This phenomenon has been observed in several previous high-altitude studies, and altitude-induced detraining could be partly responsible. *2*) If supplemental O_2 improves $\dot{V}_{O_2}$ and power output as a result of an increased Ca_{O_2}, why does the increased Ca_{O_2} observed during hematological acclimatization not also cause an improved $\dot{V}_{O_2}$ and power output compared with testing under acute hypoxic exposure? In a recent publication, we also showed that $\dot{V}_{O_2\,max}$ does not increase as much as would be expected with acclimatization and suggested that this is caused by altered distribution of blood flow at exercise after chronic exposure to high altitude compared with acute hypoxic exposure (6). Thus the fraction of cardiac output allocated to active muscle during heavy exercise is apparently smaller after chronic than after acute hypoxic exposure.

In summary, pulmonary gas exchange is substantially improved in lowlanders after 2 and 8 wk acclimatization to 4,100 m. However, even after 8 wk of acclimatization, the pulmonary gas exchange of the lowlanders remains inferior compared with that of the high-altitude natives. This is reflected by a lower $A\text{-}aP_{O_2}$ and less arterial desaturation in the natives. At high altitude, in acclimatized lowlanders and Aymara high-altitude natives, $\dot{V}_{O_2\,max}$ and W_{max} may be improved slightly but significantly by an increased O_2 supply.

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