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

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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 O2 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 O2 (Pao2) 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). Pao2 in lowlanders reached levels that were not different from those in high-altitude natives (66 ± 1.2 mmHg). Arterial O2 saturation (SaO2) 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, SaO2 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 O2 after 8W: 59 ± 4, 58 ± 4, and 52 ± 4 1·min−1·l−1, respectively. The ventilatory equivalent of O2 reached levels not different from that of Aymaras (51 ± 3 1·min−1·l−1) after 8W. However, increases in exercise alveolar Po2 and Pao2 with acclimatization had no net effect on alveolar-arterial Po2 difference in lowlanders (10 ± 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 Po2 difference (A-aPo2) at maximum exercise, thus preserving arterial Po2 (Pao2) and saturation (SaO2). 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-aPo2 was observed in the natives, whereas the lowlanders seemed to reduce their exercise A-aPo2 as the altitude exposure was prolonged (8). More recently, Calbet et al. (5, 6) also found reduced exercise A-aPo2 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-aPo2 during maximal exercise than the well-acclimatized lowlanders (25).

In the present study, three variables are considered indicators of pulmonary gas exchange: A-aPo2, ventilatory equivalent [ventilation (Ve)/O2 consumption (VO2)], and SaO2. 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 Aymara 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 Media.

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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% O2 in N2, acute hypoxia (AH)]. At 38% O2 in N2 (2WN), the second test period at sea level conditions: 38% O2 in N2 (2WN). The second test period at sea level conditions: 38% O2 in N2 (2WN).

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 O2-supplemented gas mixture [inspiratory O2 fraction (FIO2) = 0.38].

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

<table>
<thead>
<tr>
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<th>Lowlanders (n = 6)</th>
<th>Aymaras (n = 8)</th>
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<tr>
<td></td>
<td>SL</td>
<td>AH</td>
</tr>
<tr>
<td>Hb, g/l</td>
<td>139 ± 2</td>
<td>131 ± 4</td>
</tr>
<tr>
<td>Hct, %</td>
<td>42.4 ± 0.7</td>
<td>41.4 ± 0.9</td>
</tr>
<tr>
<td>Pao2, mmHg</td>
<td>93 ± 2.1</td>
<td>45 ± 0.9*</td>
</tr>
<tr>
<td>Sao2, %</td>
<td>98.4 ± 0.1</td>
<td>87.9 ± 0.6*</td>
</tr>
<tr>
<td>PcO2, mmHg</td>
<td>191 ± 3.3</td>
<td>160 ± 6*</td>
</tr>
<tr>
<td>PaCO2, mmHg</td>
<td>39 ± 1.3</td>
<td>36 ± 0.5</td>
</tr>
<tr>
<td>pH</td>
<td>7.41 ± 0.01</td>
<td>7.44 ± 0.01</td>
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</table>

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, hematocrit; Pao2, arterial P2; Sao2, arterial O2 saturation; PaCO2, arterial O2 content; Pao2, arterial P2; *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 VO2 and power output. In lowlanders at sea level, acute hypoxia caused maximal VO2 (VO2max) and power output (Wmax) to decrease by 20 and 22%, respectively (Table 2). At high altitude, VO2max and Wmax had decreased further after 2 wk but recovered after 8 wk. When VO2max and Wmax were expressed relative to body weight, no significant differences were found between acute hypoxia and the high-altitude trials [VO2max = 45 ± 1, 44 ± 1, and 47 ± 1 ml·min⁻¹·kg⁻¹ in AH, 2W, and 8W, respectively, P = not significant (NS); Wmax = 3.7 ± 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 (FiO2 = 0.38) enhanced VO2max and Wmax in the lowlanders by 13 and 15% at 2 wk and 8 wk, respectively, and by 7% in the high-altitude natives.

VO2max and Wmax were lower in the high-altitude natives than in the lowlanders. When expressed relative to body weight, VO2max and Wmax 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 O2 supply to the lungs (FiO2 = 0.38) significantly increased VO2max and Wmax, even in high-altitude natives.

Pulmonary gas exchange and arterial oxygenation. In lowlanders at sea level, acute hypoxia reduced alveolar P O2 (P A O2), PaO2, and S a O2 during maximal exercise (Table 2, Fig. 1). The decrease in S a O2 during exercise compared with rest was ~15%. This deoxygenation occurred despite a 12% increase in V E. There was a 40% increase in V E/VO2max, accompanied by a nonsignificant increase in A-aP O2.

In lowlanders at high altitude, 2 wk of acclimatization caused an increase of P A O2 during maximal exercise (by 8 mmHg, P < 0.05) and a trend toward improved PaO2 compared with acute hypoxia. The decrease in S a O2 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, PaO2, P A O2, and S a O2 continued to improve significantly compared with 2 wk. After 8 wk at high altitude, the decrease in S a O2 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 Ve after 2 and 8 wk, respectively. Ve/VO2max was significantly decreased only after 8 wk. There was no significant change in A-aP O2 in the lowlanders at high altitude. Increasing O2 supply (FiO2 = 0.38) prevented desaturation during exercise. At FiO2 = 0.38, PaO2 was higher than at sea level. Despite supranormal PaO2, Ve and A-aP O2 did not change significantly, whereas Ve/VO2max 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 O2 and PaO2 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 S a O2 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 S a O2 in high-altitude natives was not different from the 8-wk value in the lowlanders. The lower maximal Ve in the high-altitude natives was due to their smaller frames. Ve/VO2max in high-altitude natives was not significantly different from that in lowlanders after 8 wk. However, A-aP O2 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, Wmax per kilogram of body weight was similar in the high-altitude natives and the lowlanders. When expressed as Wmax/V E, the values were also similar in the two groups during the high-altitude trials (1.4 ± 0.6, 1.6 ± 0.6, and 1.6 ± 0.1 W·min⁻¹·kg⁻¹ at 2 and 8 wk and in high-altitude natives, respectively, P = NS).

P CO2, pH, and Hb O2 affinity. In lowlanders at sea level, P a CO2 was reduced during hypoxia at rest and during exercise (Tables 1 and 2). Arterial pH was higher during hypoxia than after 8 wk of acclimatization, although there was no further increase in Hb and Hct, PaO2, P a O2, and S a O2.

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 O2 supply (FiO2 = 0.38) to achieve normoxemia in lowlanders and high-altitude natives

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<tr>
<td></td>
<td>SL</td>
<td>AH</td>
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<tr>
<td>VO2max, l/min⁻¹</td>
<td>4.5 ± 0.1</td>
<td>3.7 ± 0.1f</td>
</tr>
<tr>
<td>Wmax, W</td>
<td>294 ± 12</td>
<td>302 ± 9f</td>
</tr>
<tr>
<td>V̇ E, l/min⁻¹</td>
<td>193 ± 5</td>
<td>215 ± 8f</td>
</tr>
<tr>
<td>V̇ E/VO2max</td>
<td>43 ± 5</td>
<td>59 ± 4f</td>
</tr>
<tr>
<td>P A O2, mmHg</td>
<td>113 ± 0.8</td>
<td>61 ± 0.2f</td>
</tr>
<tr>
<td>PaO2, mmHg</td>
<td>109 ± 2.9</td>
<td>51 ± 1f</td>
</tr>
<tr>
<td>A-aP O2, mmHg</td>
<td>4 ± 3.5</td>
<td>10 ± 3.5</td>
</tr>
<tr>
<td>S a O2, %</td>
<td>96 ± 1.1</td>
<td>73 ± 1.4f</td>
</tr>
<tr>
<td>P a CO2, mmHg</td>
<td>34 ± 0.7</td>
<td>29 ± 0.5f</td>
</tr>
<tr>
<td>pH</td>
<td>7.21 ± 0.2</td>
<td>7.27 ± 0.03</td>
</tr>
<tr>
<td>Tba, °C</td>
<td>39.3 ± 0.2</td>
<td>38.4 ± 0.1</td>
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Values are means ± SE. Blood gas data are corrected to femoral vein temperatures. Nat, Aymaras; 2 WN, 8WN, and NatN, increased O2 supply (inspiratory O2 fraction = 0.38) to achieve normoxemia; VO2, O2 uptake; Ve, pulmonary ventilation; Ve/VO2max, ventilatory equivalent; Wmax, power output; P a O2, arterial P O2; P A O2, arterial-arterial P O2 difference; S a O2, arterial O2 saturation; P a CO2, arterial P CO2; Tba, femoral vein blood temperature; *P < 0.05 vs. 2W. **P < 0.05 vs. AH. *P < 0.05 vs. Nat. **P < 0.05 vs. 2W. *P < 0.05 vs. 0.38 normoxia vs. hypoxia in 2W, 8W, and Nat. *P < 0.05 vs. SL.
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 \( P_{aCO_2} \) during exercise but no change in pH.

In high-altitude natives, resting \( P_{aCO_2} \), \( pH \), 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 \( P_{aCO_2} \), 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 \( V_{E}/V_{O_2} \) 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, \( V_{E}/V_{O_2} \) decrease and \( SaO_2 \) 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 high-altitude natives improve \( V_{O_2} \) 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, \( SaO_2 \) and \( V_{E}/V_{O_2} \) were significantly improved between 2 and 8 wk of exposure to altitude. This improvement in pulmonary \( V_{O_2} \) 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 \( P_{aCO_2} \) 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

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**Table 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 \( [ventilation (V_{E})/O_2 \text{ uptake (V}_{O_2})]/lI_O_2] \). B: alveolar-arterial \( P_{O_2} \) difference \( A-aP_{O_2} \). C: arterial \( O_2 \) saturation \( (SaO_2) \). Values are means ± SE.

- \( *P < 0.05 \) vs. SL; \( bP < 0.05 \) vs. acute hypoxia; \( cP < 0.05 \) vs. natives; \( dP < 0.05 \) vs. 2W.
the calculated PaO₂ 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-aPO₂ (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-aPO₂ 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-aPO₂ of ~5 mmHg in Aymara Indians taken acutely from 4,100 to 5,260 m (25). The explanation for the lower A-aPO₂ 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 PaO₂. 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-aPO₂ 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 PaO₂.

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-aPO₂ between lowlanders and Aymara high-altitude natives. The 1-mmHg A-aPO₂ 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-aPO₂. 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 O₂ at high altitude, pulmonary arterial pressures during rest and exercise are significantly lowered (14). In the present study, supplemental O₂ decreased A-aPO₂ 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-aPO₂ in lowlanders than in high-altitude natives.

It is an interesting contrast to the persistent difference in A-aPO₂ that Ve/VO₂ improved during acclimatization of the lowlanders to a level not distinguishable from that of the high-altitude natives. Thus, despite a higher A-aPO₂, the ventilation required for a given VO₂ 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 Ve/VO₂ 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 Ve/VO₂ 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 \(S_{A0}\) 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 \(V\dot{O}/V\dot{O}_2\) 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), \(V\dot{O}_2\max\) 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 \(V\dot{O}_2\max\) 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 \(V\dot{O}_2\max\) 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 \(V\dot{O}_2\) 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-a\(PO_2\) 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’ \(V\dot{O}_2\max\) 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’ \(V\dot{O}_2\max\) 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 \(V\dot{O}_2\) and power output observed in the Danish subjects presents two questions: 1) Why does \(O_2\) supplementation fail to normalize \(V\dot{O}_2\) and power output to sea level values, despite supranormal arterial \(O_2\) content (\(C_{\dot{A}O_2}\))? 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 \(V\dot{O}_2\) and power output as a result of an increased \(C_{\dot{A}O_2}\), why does the increased \(C_{\dot{A}O_2}\) observed during hematological acclimatization not also cause an improved \(V\dot{O}_2\) and power output compared with testing under acute hypoxic exposure? In a recent publication, we also showed that \(V\dot{O}_2\max\) 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-a\(PO_2\) and less arterial desaturation in the natives. At high altitude, in acclimatized lowlanders and Aymara high-altitude natives, \(V\dot{O}_2\max\) and \(W_{max}\) may be improved slightly but significantly by an increased \(O_2\) supply.

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