Why is $V_{\text{O}_2 \text{max}}$ after altitude acclimatization still reduced despite normalization of arterial O$_2$ content?

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Calbet, J. A. L., R. Boushel, G. Rádegran, H. Søndergaard, P. D. Wagner, and B. Saltin. Why is $V_{\text{O}_2 \text{max}}$ after altitude acclimatization still reduced despite normalization of arterial O$_2$ content? Am J Physiol Regul Integr Comp Physiol 284: R304–R316, 2003. First published October 3, 2002; 10.1152/ajpregu.00156.2002.—Acute hypoxia (AH) reduces maximal O$_2$ consumption ($V_{\text{O}_2 \text{max}}$), but after acclimatization, and despite increases in both hemoglobin concentration and arterial O$_2$ saturation that can normalize arterial O$_2$ concentration ([O$_2$]), $V_{\text{O}_2 \text{max}}$ remains low. To determine why, seven lowlanders were studied at $V_{\text{O}_2 \text{max}}$ (cycle ergometry) at sea level (SL), after 9–10 wk at 5,260 m (chronic hypoxia [CH]), and 6 mo later at SL in AH (FIO$_2$ 0.105) equivalent to 5,260 m. Pulmonary and leg indexes of O$_2$ transport were measured in each condition. Both cardiac output and leg blood flow were reduced by ~15% in both AH and CH ($P < 0.05$). At maximal exercise, arterial [O$_2$] in AH was 31% lower than at SL ($P < 0.05$), whereas in CH it was the same as at SL due to both polycythemia and hyperventilation. O$_2$ extraction by the legs, however, remained at SL values in both AH and CH. Although at both SL and in AH, 76% of the cardiac output perfused the legs, in CH the legs received only 67%. Pulmonary $V_{\text{O}_2 \text{max}}$ (4.1 ± 0.3 l/min at SL) fell to 2.2 ± 0.1 l/min in AH ($P < 0.05$) and was only 2.4 ± 0.2 l/min in CH ($P < 0.05$). These data suggest that the failure to recover $V_{\text{O}_2 \text{max}}$ after acclimatization despite normalization of arterial [O$_2$] is explained by two circulatory effects of altitude: 1) failure of cardiac output to normalize and 2) preferential redistribution of cardiac output to nonexercising tissues. Oxygen transport from blood to muscle mitochondria, on the other hand, appears unaffected by CH.

cardiac output; fatigue; performance; exercise; cardiovascular physiology; maximal oxygen consumption

$V_{\text{O}_2 \text{max}}$ is reduced in the same proportion as $C_{\text{A}_2}$ is lowered. Despite the reduction in maximal cardiac output in chronic hypoxia (CH) (35, 40), systemic O$_2$ delivery ($C_{\text{A}_2} \times$ cardiac output) increases to values close to those observed at SL owing to the greater blood hemoglobin concentration ([Hb]) and arterial O$_2$ saturation ($S_{\text{A}_2}$) after acclimatization (8, 47). However, $V_{\text{O}_2 \text{max}}$ either remains at the same level as in AH or increases only slightly with acclimatization (5, 8, 40, 47). Thus, there is a dissociation between maximal systemic O$_2$ delivery and $V_{\text{O}_2 \text{max}}$ during exercise in hypoxia after altitude acclimatization, the mechanisms of which remain unknown.

A reduction in muscular oxidative capacity with altitude acclimatization seems unlikely because hypoxia at altitude immediately restores SL $V_{\text{O}_2 \text{max}}$ (5, 8, 40, 47). It has been suggested that altitude acclimatization could impair O$_2$ diffusion from the capillaries to the muscular mitochondria (5, 8, 40, 47), despite that the off-loading and diffusion of O$_2$ from hemoglobin to the muscular mitochondria are facilitated by two consequences of acclimatization, a rightward shift of the O$_2$-hemoglobin dissociation curve (12, 41) and an increase in capillary density (28).

An alternative explanation is the possibility of an alteration in the distribution of blood flow between tissues competing for O$_2$ during intense exercise in CH reducing blood flow to the muscles. At altitudes up to 4,000 m, peak leg blood flow (LBF) has been reported to equal that observed in normoxia (5, 42), suggesting this is not a tenable explanation. However, to date, no studies have examined how the available cardiac output is partitioned to contracting muscle and other tissues during maximal exercise after acclimatization to higher altitudes.

The aim of this investigation was to determine why $V_{\text{O}_2 \text{max}}$ is not improved (or only marginally increased) after acclimatization to high altitude by studying the impact that altitude acclimatization has on the differ-

THE REASON WHY maximal O$_2$ consumption ($V_{\text{O}_2 \text{max}}$) and maximal exercise capacity remain substantially reduced after high-altitude acclimatization, despite arterial O$_2$ content ($C_{\text{A}_2}$) increasing to match or even surpass the values observed at sea level (SL), is unknown (5, 8, 40, 47). In moderate acute hypoxia (AH),...
ent steps composing the O₂ transport system. The two main possibilities are 1) reduction in the maximal delivery of O₂ to the exercising muscles due to changes in peak muscular blood flow and/or the distribution of cardiac output and 2) alterations in the diffusion or utilization of O₂ by the active muscles. To explore these mechanisms, the cardiovascular response to exercise was studied in healthy humans after 9–10 wk of permanence at 5,260 m, in Chacaltaya (Bolivia), in conditions of hypoxia and at least 6 mo later in AH equivalent to 5,260 m.

METHODS

Subjects

Seven healthy Danish lowlanders (3 females and 4 males) volunteered to participate in these studies. Their mean (±SE) age, height, and weight were 24.0 ± 0.6 yr, 176 ± 3 cm, and 74 ± 4 kg, respectively. The health status of each subject was assessed by a complete medical history and physical examination. All had a normal resting ECG, as well as normal liver, kidney, and thyroid function and normal fasting plasma glucose and electrolyte concentrations. Iron status was also normal for males and females as reflected by blood [Hb] (145 ± 6 and 122 ± 2 g/l) and transferrin (31.3 ± 0.3 and 32.7 ± 1.9 μmol/l). However, plasma concentrations of ferritin were normal for males and slightly reduced in two of the females (74 ± 23 and 24 ± 11 μg/l). 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. The “Guiding Principles for Research Involving Animals and Human Beings” of the American Physiological Society were strictly followed (2).

Experimental Design

As part of preliminary examinations ~2 mo before altitude exposure, subjects performed an incremental exercise test to exhaustion on a cycle ergometer (120-W initial work rate increased by 40 W every 1 min). VO₂max averaged 61 ± 0.5 ml·kg⁻¹·min⁻¹ for the males and 50 ± 3 ml·kg⁻¹·min⁻¹ for the females.

CH tests were conducted at altitude after 9- to 10-wk residence at 5,260 m on Mount Chacaltaya, Bolivia. During this time, two short expeditions (2–4 days) were carried out to peaks at 6,080 (Monte Potosi) and 6,500 m (Monte Illimani), respectively. The latter expedition took place 3–5 days before the start of the experiments. AH tests at SL were carried out at least 6 mo after the subjects returned to Denmark, after just a few minutes exposure to hypoxic gas.

Subjects performed upright, submaximal, and maximal cycling exercise at altitude and at SL with two different fractions of inspired O₂ (FIO₂). During the experiments at altitude, the subjects inspired room air (408 mmHg, P(O₂) = 76 mmHg) and air from a premixed tank containing 55% O₂ in nitrogen (P(O₂) = 200 mmHg). Experiments at SL were carried out at a barometric pressure of 750–760 mmHg with two different levels of FIO₂, 0.210 (room air) and 0.105 (from a premixed tank of O₂ in nitrogen). The latter resulted in a P(O₂) similar to that observed at altitude (i.e., 75 mmHg).

Exercise Protocol

Two different kinds of exercise tests were performed: submaximal constant intensity and incremental exercise on the cycle ergometer (Monark 824 E, Vadberg, Sweden) until exhaustion. Thirty minutes after catheterization, subjects sat on the cycle ergometer and breathed through a two-way valve inspiring room air (CH) or 10.5% O₂ (AH) for 5 min before rest measurements were made (Fig. 1). Subjects then cycled at the highest intensity they could tolerate for 10 min (known from preliminary tests) when exercising in AH (102–141 W, at 80 revolutions/min). Measurements were made at 6 and 10 min. Subsequently, after resting for ~10 min in CH and 20–30 min in AH, the maximal exercise test was started at an initial intensity identical to that used in the submaximal test. This was maintained for 2 min. Exercise intensity was then increased rapidly to 90% of previously determined peak levels (Wmax). After 2 min, measurements were made and the load was increased as tolerated to maximal levels by ~20–40 W every min until reaching the maximal exercise...
intensity (Wmax). Load increments were adjusted such that the exercise duration of the incremental exercise tests was ~6–7 min in all conditions. Just at the end of the exercise with hypoxia, subjects were vigorously encouraged to keep pedaling while they were switched to breathe hypoxic air (FIO2 = 0.55), giving a P02 of ~200 mmHg in CH, or room air at SL in the AH study. After 2 min at this P02, a further set of measurements was made, and finally the workload was increased again in steps of 20–40 W every min, and close to exhaustion measurements were repeated. In this way, the same protocols and O2 exposure profiles were used in both AH and CH.

**Measurements**

**Respiratory variables.** Pulmonary V02, CO2 production (VCO2), and expired minute ventilation (Ve) were measured continuously with an on-line system (Medical Graphics CPX, Saint Paul, Minneapolis, MN) and averaged every 15 s. Gases with known O2 and CO2 concentrations (micro-Scholander) were used for gas analyzer calibration before every test. During submaximal exercise, the V02 values obtained during the last 4 min were averaged. During the incremental exercise, the highest V02 value recorded during any single 15-s interval was taken as the V02 max. The system operated only when ambient air was breathed, and thus no data were obtained in hypoxia (i.e., 55% in CH).

**Blood flow.** Femoral venous blood flow (i.e., LBF) was measured in the femoral vein by constant-infusion thermodilution as described in detail in our companion article (3). Briefly, iced saline was infused through the femoral vein catheter at flow rates sufficient to decrease blood temperature at the thermistor by 0.5–1°C. Infusate and blood temperature were measured continuously during saline infusion (Harvard pump, Harvard Apparatus, Millis, MA) via thermistors connected to the data-acquisition system (MacLab 16/s ADInstruments, Sydney, Australia). Blood flow was calculated on thermal balance principles, as detailed by Andersen and Saltin (3). Resting blood flows were measured in triplicate and averaged. During submaximal exercise, blood flow was measured twice, at 6 and 9 min. The reported value for each exercise load represents the average of the four measurements. At peak effort, the measurements were made within 1 min of exhaustion. When possible, duplicate measurements of LBF and femoral arteriovenous O2 differences were made during the brief period of peak exercise. Heart rate (HR), arterial blood pressure, pulmonary VO2, VCO2, and Ve were measured at the same time as LBF and cardiac output.

**Blood pressure and HR.** Intra-arterial blood pressure was measured with a disposable transducer (T100209A, Baxter, Unterschleissheim, Germany) placed at the level of the inguinal ligament. A three-lead ECG was used to measure HR and displayed on a monitor (Dialogue 2000, Danica, Copenhagen, Denmark) during the experimental and recovery phases. The blood pressure and ECG signals were recorded with the data-acquisition system. Systolic and diastolic arterial pressures were computed from the recorded pressure wave, as the maximum and minimum values registered in each cardiac cycle. Mean arterial blood pressure (MAP) was calculated as the integral of the pressure-wave curve over time. Average values corresponding to the blood flow measurement period were recorded for further calculations.

**Cardiac output.** Cardiac output was measured by indocyanine green (Akorn) dye-dilution (14), as described in detail in our companion article.

**Blood Analysis**

Blood [Hb] and O2 saturation (SO2) were measured with a cooximeter (OSM 3 Hemoximeter, Radiometer, Copenhagen, Denmark). P02, PCO2, and pH were determined with a blood gas analyzer (ABL 5, Radiometer). From these values, plasma HCO3 and actual base excess (BE) were determined as described by Sigggaard-Andersen (43). As reduced Hb has a higher buffer capacity than fully oxygenated, BE was adjusted in each blood sample to fully oxygenated Hb (BEadj) (43). Hematocrit was determined by microcentrifugation on triplicate samples. Arterial and venous venous O2 content (CaO2 and CvO2) were computed from the saturation and [Hb] (i.e., 1.34[Hb] × SO2 + 0.003 × P02). Plasma K+ and blood lactate and glucose were measured with an electrolyte metabolite analyzer (EML 105, Radiometer). Plasma norepinephrine and epinephrine concentrations were measured by HPLC with electrochemical detection (21).

**Calculations**

Arteriovenous O2 concentration ([O2diff]) difference (a-V02diff) was calculated from the difference in femoral arterial and venous femoral [O2]. This difference was then divided by arterial concentration to give O2 extraction. Oxygen delivery was computed as the product of blood flow and CaO2. Leg VO2 was calculated as the product of LBF and a-V02diff. Non-leg VO2 was calculated as the difference between pulmonary VO2 and 2 × leg VO2. Leg plasma flow (LPF) was calculated as the product of LBF and (1 – hematocrit). Net leg lactate and potassium release were calculated as the product of LBF and LPF, the venous-arterial difference of blood lactate, and plasma K+ concentrations, respectively. The standard P02, defined as the values of P02 that cause hemoglobin to be saturated by 50% when the O2-Hb equilibrium curve is determined at 37°C, pH = 7.40, PCO2 = 40 mmHg, was calculated from the whole set of arterial and venous gases obtained in each experiment for the acclimatized and unacclimatized state. Blood gas variables were corrected to and expressed at body temperature.

**Statistical Analysis**

Differences in the measured variables among conditions and exercise levels were analyzed with two-way ANOVA for repeated measures, with altitude acclimatization and exercise intensity as within-subjects factors. When F was significant in the ANOVA, planned pair-wise-specific comparisons were carried out using Student’s paired t-test adjusted for multiple comparisons with the Bonferroni procedure. Simple linear regression analysis was performed to determine linear relations between variables. Significance was accepted at P < 0.05. The influence of altitude acclimatization on the slope of the relationship between blood flow and cardiac output was assessed using analysis of covariance, with blood [Hb] as covariate. Data are reported as means ± SE.

**RESULTS**

**Blood Gases and Acid-Base Balance**

Exposure to altitude and AH resulted in similar significant decreases in PaO2 and SaO2 at rest (Table 1). During AH, this led to a significant decrease in CaO2. Nine- to 10-wk exposure to high altitude, however, increased blood [Hb] by 36% compared with that at SL (182 ± 0.4 vs. 135 ± 5 g/l). As a result, despite the decreases in PaO2 and SaO2, CaO2 at rest after acclima-
Table 1. Femoral arterial and venous blood gases and acidbase balance at rest and during submaximal and maximal exercise during acute and chronic hypoxia

<table>
<thead>
<tr>
<th></th>
<th>Rest Acute hypoxia</th>
<th>Rest Chronic hypoxia</th>
<th>Submaximal Exercise Acute hypoxia</th>
<th>Submaximal Exercise Chronic hypoxia</th>
<th>Maximal Exercise Acute hypoxia</th>
<th>Maximal Exercise Chronic hypoxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity, W</td>
<td>0</td>
<td>0</td>
<td>121 ± 4</td>
<td>118 ± 5</td>
<td>207 ± 8</td>
<td>231 ± 17</td>
</tr>
<tr>
<td>PO₂, mmHg</td>
<td>72 ± 0</td>
<td>76 ± 0</td>
<td>72 ± 0</td>
<td>76 ± 0</td>
<td>72 ± 0</td>
<td>76 ± 0</td>
</tr>
<tr>
<td>Art Hb, g/d</td>
<td>138 ± 6</td>
<td>180 ± 2*</td>
<td>140 ± 5</td>
<td>185 ± 6*</td>
<td>138 ± 6</td>
<td>188 ± 6*</td>
</tr>
<tr>
<td>Ven Hb, g/d</td>
<td>144 ± 5</td>
<td>186 ± 2*</td>
<td>142 ± 5</td>
<td>187 ± 6*</td>
<td>139 ± 6</td>
<td>190 ± 6*</td>
</tr>
<tr>
<td>PO₂, mmHg</td>
<td>47 ± 4</td>
<td>49 ± 0</td>
<td>31 ± 1</td>
<td>44 ± 1*</td>
<td>34 ± 1</td>
<td>45 ± 1*</td>
</tr>
<tr>
<td>PİV0₂, mmHg</td>
<td>24 ± 2</td>
<td>25 ± 1</td>
<td>10 ± 1</td>
<td>15 ± 1*</td>
<td>10 ± 1</td>
<td>14 ± 1*</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>82.3 ± 3.1</td>
<td>85.0 ± 0.5</td>
<td>63.0 ± 1.9</td>
<td>75 ± 2.9*</td>
<td>67.8 ± 2.5</td>
<td>72.5 ± 2.9</td>
</tr>
<tr>
<td>SlV0₂, %</td>
<td>47.4 ± 4.9</td>
<td>42.6 ± 1.7</td>
<td>9.5 ± 2</td>
<td>12.1 ± 1.9*</td>
<td>8.2 ± 1.7</td>
<td>8.9 ± 1.9</td>
</tr>
<tr>
<td>CaO₂, ml/l</td>
<td>166 ± 9</td>
<td>218 ± 3*</td>
<td>124 ± 6</td>
<td>196 ± 11*</td>
<td>132 ± 8</td>
<td>192 ± 10*</td>
</tr>
<tr>
<td>CİV0₂, ml/l</td>
<td>92 ± 12</td>
<td>108 ± 4*</td>
<td>19 ± 5</td>
<td>32 ± 5*</td>
<td>17 ± 4</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>27 ± 2</td>
<td>22 ± 0*</td>
<td>27 ± 1</td>
<td>21 ± 1*</td>
<td>26 ± 1</td>
<td>20 ± 1*</td>
</tr>
<tr>
<td>PİVCO₂, mmHg</td>
<td>42 ± 2</td>
<td>31 ± 1*</td>
<td>49 ± 1</td>
<td>41 ± 2</td>
<td>49 ± 1</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Art pH</td>
<td>7.53 ± 0.03</td>
<td>7.47 ± 0.06</td>
<td>7.42 ± 0.01</td>
<td>7.41 ± 0.02</td>
<td>7.39 ± 0.02</td>
<td>7.37 ± 0.02</td>
</tr>
<tr>
<td>Venous pH</td>
<td>7.42 ± 0.01</td>
<td>7.43 ± 0.00</td>
<td>7.33 ± 0.02</td>
<td>7.31 ± 0.02</td>
<td>7.25 ± 0.02</td>
<td>7.21 ± 0.02</td>
</tr>
<tr>
<td>Art HCO₃⁻, mmol/l</td>
<td>20.3 ± 1.6</td>
<td>15.9 ± 0.2*</td>
<td>17.0 ± 1.2</td>
<td>12.9 ± 0.8*</td>
<td>15.4 ± 1.0</td>
<td>10.9 ± 0.4*</td>
</tr>
<tr>
<td>Ven HCO₃⁻, mmol/l</td>
<td>25.3 ± 1.2</td>
<td>20.3 ± 0.4*</td>
<td>21.6 ± 1.2</td>
<td>20.3 ± 1.0</td>
<td>20.8 ± 1.1</td>
<td>19.1 ± 0.8*</td>
</tr>
<tr>
<td>Art BE, mmol/l</td>
<td>1.5 ± 0.7</td>
<td>-3.4 ± 0.2*</td>
<td>-5.5 ± 1.2</td>
<td>-7.1 ± 1.1</td>
<td>-7.3 ± 1.3</td>
<td>-9.6 ± 0.7*</td>
</tr>
<tr>
<td>Ven BE, mmol/l</td>
<td>0.9 ± 0.7</td>
<td>-3.8 ± 0.1*</td>
<td>-6.1 ± 1.2</td>
<td>-8.1 ± 1.2</td>
<td>-8.7 ± 1.3</td>
<td>-11.5 ± 0.8*</td>
</tr>
<tr>
<td>Art La, mmol/l</td>
<td>5.9 ± 0.8</td>
<td>1.6 ± 0.0*</td>
<td>6.2 ± 1.1</td>
<td>4.9 ± 0.7</td>
<td>8.2 ± 0.5</td>
<td>8.8 ± 1.1</td>
</tr>
<tr>
<td>Ven La, mmol/l</td>
<td>0.8 ± 0.8</td>
<td>1.4 ± 0.1*</td>
<td>6.4 ± 1.2</td>
<td>5.1 ± 0.8</td>
<td>8.5 ± 0.5</td>
<td>10.4 ± 1.2</td>
</tr>
</tbody>
</table>

Values are means ± SE. All venous data reflect femoral venous samples. Resting values in hypoxia were obtained in 6 subjects of similar characteristics, after 3–5 min breathing a hypoxic gas mixture containing 10.5% O₂ in N₂. Art, arterial; Ven, venous; BE, base excess; La, lactate. *P < 0.05 compared with the same condition in acute hypoxia; †P < 0.05 compared with the same condition without attitude acclimatization; ‡P < 0.05 compared with maximal exercise in chronic hypoxia.

Acclimatization to altitude was 19% higher than it was during normoxia at SL (218 ± 6 vs. 180 ± 2 mmHg). Compared with AH, acclimatization resulted in lower resting values of PaCO₂, PICO₂, pHₐ, arterial and venous HCO₃⁻ as well as lower arterial (ABEadj) and venous (VBEadj) adjusted BE (Table 1).

As expected, Pao₂ and SaO₂ during exercise were significantly reduced in both CH and AH (Table 1). However, the decreases during AH were greater than those in CH. Consequently, CaO₂ decreased with exercise intensity but more steeply in AH than in CH. Femoral venous blood gases (SfcO₂, PfcO₂, and CfcO₂) during exercise were markedly reduced, an effect that was accentuated in AH compared with CH (Table 1). Although exercise resulted in a fall in arterial pH, the decrease during AH was blunted slightly compared with CH. CH and AH each resulted in parallel reductions in arterial plasma HCO₃⁻, ABEadj, and PaCO₂ during exercise, responses that were greater after altitude acclimatization than they were with AH (Table 1).

P₅₀ values (expressed at 37°, for pH = 7.40 and Pco₂ = 40 mmHg) were increased from 24.5 ± 0.3 at SL (AH) to 30.5 ± 0.6 after altitude acclimatization.

Pulmonary Gas Exchange, Cardiac Output, and Systemic O₂ Delivery

Although pulmonary ventilation remained unchanged during submaximal exercise (Fig. 2A), the alveolar Po₂ was increased by 9% (Fig. 2B) while the A-aDO₂ was reduced by 39% (Fig. 2C) with acclimatization. Consequently, submaximal exercise arterial oxygenation was substantially improved as reflected by enhancement of PaO₂ (43%) and SaO₂ (19%) with acclimatization (Table 1).

Submaximal exercise pulmonary VO₂ was similar in AH and CH (Fig. 2D), despite a 15% lower cardiac output after acclimatization, which, however, allowed a higher O₂ delivery than in AH due to the acclimatization-induced elevation in blood [Hb].

Maximal exercise ventilation increased by 29% with acclimatization, attaining the same value as at SL (Fig. 2A). The corresponding alveolar Po₂ was higher by 9% (Fig. 2B) and the A-aDO₂ lower by 26% (Fig. 2C), leading to improved oxygenation at maximal exercise after acclimatization, as reflected by the increase in PaO₂ (34%) and SaO₂ (7%, P = 0.33) (Table 1).

Maximal power output was not significantly increased, but maximal pulmonary VO₂ was 13% higher after acclimatization than it was in AH (Fig. 2A) (P < 0.05). However, VO₂max after acclimatization was still 26% lower than at SL (Fig. 2D). The subjects with the greatest normoxic VO₂max tended to improve their hypoxic VO₂max more with acclimatization (r = 0.66, P = 0.10).

Maximal cardiac output values were similarly reduced (i.e., by ~15%, P < 0.05) in CH and AH compared with normoxia at SL or hypoxia at altitude. The effect of CH on cardiac output, however, was rapidly and completely reversed with hypoxia at altitude (Fig. 3A). HR during submaximal and maximal exercise...
Exercise was 15–20% lower after acclimatization (Fig. 3C). This difference was halved with hyperoxic breathing at altitude. The maximal stroke volume was higher after acclimatization (Fig. 3E) \( (P < 0.01) \).

As shown in Fig. 3B, altitude acclimatization resulted in a marked increase (37–54%) in systemic \( O_2 \) delivery compared with AH. Similarly, systemic \( a-vO_2\text{diff} \) was higher during CH than AH (Fig. 3D). Consequently, systemic \( O_2 \) extraction during exercise ranged between 63 and 67% after altitude acclimatization, while it attained values close to 87% during AH (Fig. 3F) \( (P < 0.001) \). A close linear relationship was observed between exercise intensity and cardiac output \( (r = 0.98, P < 0.001) \).

### LBF, Leg \( \dot{V}O_2 \), and Muscle-Diffusing Capacity

Blood flow to the legs during submaximal and maximal exercise was slightly reduced in CH compared with AH but differences did not reach statistical significance (Fig. 4A) \( (P = 0.48) \). However, the maximal LBF in CH was 25% lower than that observed in normoxia at SL \( (13.9 \pm 1.2 \text{ vs. } 18.4 \pm 0.5 \text{ l/min, } P < 0.01) \).

Despite this reduction in maximal LBF with hypoxia, maximal oxygen delivery to the legs during hypoxia was higher by 40% in CH than AH (Fig. 4C). However, it was still 24% lower than that observed in normoxia at SL. This increase in leg \( O_2 \) delivery was reflected in significant differences in femoral \( a-vO_2\text{diff} \) between CH and AH (Fig. 4B). The fraction of \( O_2 \) extracted by the legs was similar in CH and AH, while it was reduced with the hyperoxic gas at altitude (Fig. 4D).

Leg \( \dot{V}O_2 \) during submaximal and maximal exercise was increased by 42 and 39% after altitude acclimatization \( (P < 0.001) \). Peak leg \( \dot{V}O_2 \) after altitude acclimatization remained, however, 21% below the value attained in normoxia at SL (Fig. 4E) \( (P < 0.05) \). Muscle \( O_2 \) conductance (represented by the slope of the relationship between peak leg \( \dot{V}O_2 \) and capillary \( P_{O_2} \)) was similar before and after altitude acclimatization (Fig. 4F), under all conditions (except hyperoxia at altitude, where \( \dot{V}O_2\text{max} \) failed to increase in proportion to capillary \( P_{O_2} \)).

In addition, leg \( \dot{V}O_2 \) was closely related to leg \( O_2 \) delivery \( (r = 1, P < 0.001) \) as was LBF to cardiac output \( (r = 0.86, P < 0.01) \). When the conditions with different blood [Hb] were analyzed separately, the coupling between LBF and cardiac output was even more evident, as shown in Fig. 5. Moreover, the slope of the relationship between LBF and cardiac output was less
accentuated after altitude acclimatization than in AH ($P < 0.05$).

**Distribution of Cardiac Output**

During submaximal exercise, similar proportions of cardiac output were directed to tissues other than the exercising legs in CH and AH (4.1 ± 0.5 and 5.3 ± 0.8 l/min, respectively). At maximal exercise, however, blood flow to regions other than the legs was enhanced in CH compared with AH (6.6 ± 0.8 vs. 4.8 ± 0.9 l/min, respectively, $P = 0.05$). Although at both SL and in AH, 76% of the cardiac output perfused the legs, in CH the legs received only 67%. With hyperoxic breathing at altitude, noncontracting tissue blood flow during maximal exercise was additionally increased to 8.8 ± 1.2 l/min, this value being significantly higher than that observed at maximal exercise in normoxia (4.7 ± 0.6 l/min; $P < 0.05$). Furthermore, the amount of blood flow diverted to regions other than the legs during maximal exercise also appeared to be related to $CaO_2$ as indicated by the close linear relationship between the lumped vascular conductance across these regions and $CaO_2$ ($r = 0.81$, $P = 0.05$).

**MAP, Systemic Vascular Conductance, and Leg Vascular Conductance**

MAP during exercise after altitude acclimatization was 11–13 mmHg higher than in AH (Fig. 6A). This
increase in MAP was brought about by mainly an increase in diastolic blood pressure. Compared with AH, systemic vascular conductance was reduced after acclimatization but only during submaximal exercise (Fig. 6B). Likewise, leg vascular conductance tended to be reduced after acclimatization, reaching a maximal value that was lower than that attained during maximal exercise in normoxia (Fig. 6C).

**Plasma Catecholamines**

Arterial and venous plasma norepinephrine concentrations at rest were elevated following altitude acclimatization (2.3–2.4 nmol/l) compared with those at SL after 3–5 min of AH (0.7 ± 0.1 nmol/l). During submaximal exercise, plasma norepinephrine concentrations increased similarly in CH and AH. However, when the conditions with a similar $\text{CaO}_2$ were compared (i.e., maximal exercise intensity in CH and the same intensity with normoxia), CH elicited a higher noradrenaline response (Fig. 7). Even at maximal exercise with hyperoxia after altitude acclimatization, plasma norepinephrine was slightly higher than when breathing atmospheric air ($P = 0.06$). By contrast, arterial and venous plasma concentrations of epinephrine tended to be higher after altitude acclimatization, but differences were not statistically significant. Interestingly, arterial plasma concentrations of epinephrine correlated with cardiac output ($r = 0.76, P < 0.05$).
**Blood Lactate and Potassium**

Arterial and venous blood lactate concentrations were significantly higher in both CH and AH than they were in normoxia (Table 1), leading to a higher lactate release during exercise in CH. By contrast, lactate release was significantly reduced by hyperoxic breathing. In addition, arterial blood lactate concentrations correlated with cardiac output ($r = 0.74, P < 0.05$), $\text{PaO}_2$ ($r = -0.73, P < 0.05$) and the arterial plasma concentrations of epinephrine ($r = 0.88, P < 0.01$) and norepinephrine ($r = 0.85, P < 0.01$). Net lactate release, on the other hand, correlated with the plasma arterial concentration of epinephrine ($r = 0.75, P < 0.05$).

Femoral venous plasma [K$^+$] was greater than arterial concentrations in all conditions, indicating a net release of K$^+$ that was more accentuated during submaximal exercise after altitude acclimatization than in AH ($P < 0.05$). Arterial plasma [K$^+$] was closely related to LBF ($r = 0.73, P < 0.05$), cardiac output ($r = 0.93, P < 0.01$), and arterial blood [La] ($r = 0.85, P < 0.01$). Leg potassium release, on the other hand, correlated with MAP ($r = 0.72, P < 0.05$), LBF ($r = 0.74, P < 0.05$), and cardiac output ($r = 0.82, P < 0.05$).

**DISCUSSION**

This study shows that $\dot{\text{V}}_{\text{O}}_{\text{2 max}}$ at altitude is not improved with acclimatization as much as would be expected (given the increase of the maximal capacity for $\text{O}_2$ transport to near maximal SL values) because most of the extra $\text{O}_2$ available is distributed to other tissues than the exercising muscles. The effects of altitude acclimatization on the main steps of the oxygen transport system are discussed below.

**Cardiac Output and Systemic $\text{O}_2$ Delivery**

Since the pioneer publication by Pugh et al. (35), investigators have consistently found a decrease in maximal cardiac output with CH starting at altitudes higher than 3,100 m and for exposure durations up to 5 wk, a response that is more accentuated as the altitude of the residence is increased (20, 24, 40, 47). Our study expands on these observations and demonstrates that this decrease is still present after 9–10 wk of acclimatization to high altitude. Interestingly, maximal cardiac output was reduced to the same extent in AH, which contrasts with previous studies reporting similar maximal cardiac outputs in normoxia and AH (23, 24, 44, 49). This discrepancy is likely caused by the severity of the AH exposure elicited in the present study that caused the $\text{PaO}_2$ to drop to the limit that a human can tolerate acutely (30–34 mmHg). A similar $\text{PaO}_2$, drop (to 29–31 mmHg) was reported in subjects progressively decompressed to the barometric pressure equivalent to the summit of Mt. Everest during Operation Everest II experiments (36, 47). In AH as well as in CH, SL maximal cardiac outputs were restored just by increasing $\text{PaO}_2$ and $\text{SaO}_2$ to SL or mildly hyperoxic values. This implies that the mechanism causing the reduction in maximal cardiac output is directly related to the $\text{PaO}_2$ and relatively independent of $\text{CaO}_2$.

Severe hypoxemia may account for the acute reduction in cardiac output acting directly on the heart (1) or indirectly by attenuating the output drive to the heart from the cardiovascular nuclei in the central nervous system (46). There is no evidence from this or other studies suggesting that myocardial $\text{O}_2$ supply deficit could have accounted for the reduction in maximal cardiac output, inasmuch as when the subjects were switched to breathe under normoxic or hyperoxic conditions, cardiac output did not increase until exercise intensity was augmented. In agreement, even with more severe hypoxemia, no sign of impairment in myocardial function has been reported (30, 36). The possibility of insufficient myocardial $\text{O}_2$ delivery in CH is even less plausible. Although the $\text{O}_2$ inspiratory pressures were identical, the degree of hypoxemia was considerably higher in AH than in CH likely due to the improvement of pulmonary gas exchange and ventilation with acclimatization to high altitude (48). In addition, the marked enhancement in blood [Hb] and the improvement in $\text{SaO}_2$ with acclimatization allowed for a recovery of $\text{CaO}_2$ to values similar to those observed
during maximal exercise in normoxia. With comparable $\text{Ca}_2 \text{O}_2$, myocardial $\text{O}_2$ delivery was probably also similar during exercise in CH and normoxia.

It has been proposed that the reduction in maximal cardiac output after altitude acclimatization may be caused by the reduction in maximal HR observed in CH (17, 26). A lower maximal HR does not appear to be the main mechanism responsible for the reduction in maximal cardiac output since with hyperoxia, HR was increased without significant changes in cardiac output due to the reduction of stroke volume. In addition, we recently showed that the increase of maximal HR to match at altitude the values attained at SL does not enhance maximal cardiac output or $\text{VO}_2\text{max}$ (6).

An alternative explanation is that severe hypoxemia may have altered the capacity to fully activate motor units and thus caused a decrease in maximal exercise

Fig. 6. Blood pressure and vascular conductance. Mean arterial pressure (MAP), systemic vascular conductance (VC), and 2-leg VC during submaximal and maximal exercise in acute hypoxia (•) and after 9–10 wk at 5,260 m while breathing either ambient air (■) or hyperoxic gas (○). *Significant differences between acute and chronic hypoxia ($P < 0.05$); and §significant differences between chronic hypoxia and normoxia at sea level at the same exercise intensity ($P < 0.05$).

Fig. 7. Plasma catecholamines. Arterial plasma epinephrine (bottom) and norepinephrine (top) concentrations during submaximal and maximal exercise in acute hypoxia (•) and after 9–10 wk at 5,260 m while breathing either ambient air (■) or hyperoxic gas (○). *Significant differences between acute and chronic hypoxia ($P < 0.05$); and §significant differences between chronic hypoxia and normoxia at sea level at the same exercise intensity ($P < 0.05$).

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intensity. A reduction in maximal exercise intensity would attenuate the “muscle pump” action and likely reduce venous return and, therefore, cardiac output. In favor of this hypothesis, it should be considered that cardiac output was closely related to exercise intensity in all conditions. Yet it could also be the case that centrally mediated blunting of cardiac output by low 

\( P_O_2 \) may attenuate LBF, which would in turn limit muscle work capacity.

Although maximal cardiac output was similar in AH and CH, maximal systemic \( O_2 \) delivery was considerably enhanced by acclimatization, being 54% higher after acclimatization than in AH, reaching a value that was just 11% below that attained during maximal exercise in normoxia. Nonetheless, after acclimatization, \( \dot{V}O_2_{\text{max}} \) was only 13% higher than in AH and remained 26% lower than in normoxia. If we compare, however, the improvement in \( \dot{V}O_2_{\text{max}} \) observed in the present study with, for example, the 18% increase elicited by 8 wk of training at SL in college students (39), our interpretation would have been that acclimatization resulted in a great improvement of \( \dot{V}O_2_{\text{max}} \), especially taking into account that the subjects remained physically active but did not train systematically with the aim of improving their \( \dot{V}O_2_{\text{max}} \). However, the fact that we would like to highlight is that this improvement in \( \dot{V}O_2_{\text{max}} \) is rather small compared with the remarkable improvement of systemic \( O_2 \) delivery, i.e., potentially \( \dot{V}O_2_{\text{max}} \) could have increased much more than it actually did. This finding is in accordance with previous studies showing marginal improvements or lack of change in \( \dot{V}O_2_{\text{max}} \) with acclimatization, despite substantial improvements in maximal \( O_2 \) delivery (5, 16, 40, 47).

The results of this study demonstrate that the main reason why \( \dot{V}O_2_{\text{max}} \) is not improved as would be expected given the large increase in systemic \( O_2 \) delivery with altitude acclimatization is that only a portion of the enhanced \( O_2 \) transport capacity is made available to the locomotor muscles. In AH, a major proportion of the blood flow is deviated to the working legs leaving only 4.8 l/min to supply the rest of the vascular beds. This value is slightly lower than the 5.1 reported by Kjaer et al. (30) during semirecumbent cycling exercise (\( F_I_{O_2} = 0.115 \)). It should be mentioned, however, that the intensity of the exercise used by Kjaer et al. (30) was high but not maximal. In this study, the amount of blood flow directed to noncontracting tissues in CH was 37% higher than in AH at the expense of reducing the amount of flow directed to the exercising muscles. Actually, combining all the conditions included in this study and using linear regression analysis with blood [Hb] as covariate, it became very clear that a greater proportion of the cardiac output is directed to noncontracting tissues the higher the \( C_{aO_2} \), especially at maximal exercise. As a consequence, the extra \( O_2 \)-carrying capacity of blood gained with altitude acclimatization could only be marginally exploited by the exercising muscles, which limited the improvement of \( \dot{V}O_2_{\text{max}} \) to one-third of what would have been possible if the regional distribution of blood flow during exercise in hypoxia was kept similar after altitude acclimatization to that observed in AH. This pattern allows modest improvements in maximal work capacity at altitude while ensuring improvements in the \( O_2 \) supply to noncontracting tissues.

**Regulation of LBF**

In agreement with our previous work, the bulk of our data indicates that at the same absolute exercise intensity, the elevation of \( C_{aO_2} \) is counterbalanced by a reduction in LBF (31, 32, 38) such that \( O_2 \) delivery to the working muscles is maintained. Nonetheless, our results suggest also that in acute severe hypoxia, the elevation of LBF is insufficient to completely account for the diminution in \( C_{aO_2} \) and, hence, a situation is created in which \( O_2 \) delivery does not match \( O_2 \) demand, requiring a complementary activation of anaerobic energy pathways. This is supported by the fact that during submaximal exercise, leg \( V_O_2 \) was lower in AH than in CH (52).

In AH, the amount of blood flow directed to the vascular beds apart from the contracting skeletal muscles was minimal, yet a further degree of redistribution of blood flow to the legs would have likely compromised the supply of \( O_2 \) to critical organs. Therefore, if the degree of redistribution of blood flow to the exercising muscles was maximal, or nearly maximal, the only mechanism left to increase LBF would have been an elevation of cardiac output. Compared with AH, leg vascular conductance was lower after acclimatization, but the conductance across noncontracting tissues was higher. Had this adaptation in the regulation of vascular conductances not occurred, it is clear that \( \dot{V}O_2_{\text{max}} \) in CH would have been ~11% higher than observed. Thus, the fall in \( \dot{V}O_2_{\text{max}} \) with acclimatization would have been 15%, almost matching the 11% reduction in systemic \( O_2 \) delivery observed after acclimatization. Thus, an important adaptation to high altitude is that blood flow priority is given to the low \( O_2 \) demand of the noncontracting tissues over the high metabolic demand of the exercising skeletal muscles. Given the increased maximal exercise \( V_E \) after acclimatization, a greater blood flow supply to the respiratory muscles after acclimatization is also plausible (22).

A noteworthy finding from this study is that during submaximal exercise, net K⁺ release was higher after altitude acclimatization than in AH. In contrast, exercise-net K⁺ release was similar in AH and normoxia, as previously reported (31), suggesting that this effect is a consequence of the acclimatization process. Net K⁺ release depends on the balance between K⁺ uptake and K⁺ release. Muscle K⁺ uptake depends mainly on the activity of the Na⁺-K⁺ pump, which increases with exercise intensity (9). Recent studies showed that CH is associated with a downregulation of the Na⁺-K⁺-ATPase pumps (18, 19) and increased plasma concentration of an endogenous inhibitor of Na⁺-K⁺-ATPase pumps (13) similar to ouabain (27). Both mechanisms could have led to reduced muscular K⁺ uptake after acclimatization. The potassium released from the ac-
tive muscles may act on the central chemoreceptors increasing ventilation and the sympathetic drive to the heart and muscles (33). In agreement, compared with AH, a more accentuated norepinephrine response to exercise has been observed in the present study and others (34) after altitude acclimatization.

Effect of Acclimatization on Pulmonary Gas Exchange

Although resting \( P_{\text{aO}_2} \) was similar in AH and CH, pulmonary gas exchange was impaired with exercise in both conditions but to a greater extent before than after acclimatization. As reported in our companion paper, \( P_{\text{aO}_2} \) fell from 47 mmHg at rest to 34 mmHg at maximal exercise in AH, whereas after acclimatization, \( P_{\text{aO}_2} \) decreased from 49 to 45 mmHg, i.e., the fall in \( P_{\text{aO}_2} \) was only one-third of that observed before acclimatization. Two main mechanisms accounted for this enhancement of \( P_{\text{aO}_2} \) after acclimatization: an increase in \( P_{\text{aO}_2} \) and the improvement of pulmonary gas exchange, as reflected by the reduction in the \( A-a \text{DO}_2 \) after acclimatization. The enhancement of \( P_{\text{aO}_2} \) at maximal exercise was by 5 mmHg and is probably a direct consequence of the greater maximal ventilation after acclimatization.

The 6-mmHg reduction of \( A-a \text{DO}_2 \) after acclimatization could be due to reduced ventilation-perfusion inequality and pulmonary shunt and/or increased lung-diffusing capacity (49, 50). Previous studies unequivocally showed that ventilation-perfusion mismatch accounts for a small part of the \( A-a \text{DO}_2 \) during submaximal and near-maximal exercise in AH and CH (49, 50), while shunt has been excluded as a factor contributing to the \( A-a \text{DO}_2 \) during exercise in hypoxia (49) in the absence of pulmonary edema. Therefore, an improvement in lung-diffusing capacity appears likely to be the main mechanism responsible for the decrease of \( A-a \text{DO}_2 \) with acclimatization. The total lung-diffusing capacity is composed of two main components: the membrane-diffusing capacity (\( D_{\text{mO}_2} \)) and the blood (or erythrocyte)-diffusing capacity (\( D_{\text{eO}_2} \)). The membrane-diffusing capacity is principally determined by structural factors that likely do not change with acclimatization in lowlanders. Thus, any putative improvement of diffusive conductance should be explainable by an enhancement of \( D_{\text{eO}_2} \). The blood-diffusing capacity is primarily determined by the capillary blood volume, [Hb], and hemoglobin affinity for O\(_2\) (\( P_{50} \)) (15). The 36% higher blood [Hb] would have also improved lung-diffusing capacity by reducing the spacing of red blood cells within the capillaries (25). In contrast, the increase of \( P_{50} \) with acclimatization reduces effective O\(_2\) solubility in blood for a given \( P_{\text{aO}_2} \) and, thus, could impair the erythrocytic component of total lung-diffusing capacity. In fact, the improvement in \( S_{\text{aO}_2} \) after acclimatization would have been 10% higher if the \( P_{50} \) had remained unchanged with acclimatization, as illustrated in Fig. 8. Because arterial pH and blood temperature were rather similar at maximal exercise in AH and CH, the left shift effect elicited by the respiratory alkalosis was counterbalanced after acclimatization by the increase in \( P_{50} \), bringing the oxyhemoglobin dissociation curve to the same position as that observed in normoxia before acclimatization (see Fig. 7 of our companion paper).

Another factor that could have also influenced gas exchange after acclimatization is the time available for diffusion equilibration between the alveoli and the pulmonary capillaries, which depend on the mean transit time of blood across the alveolar capillary bed (4). Although the fact that maximal cardiac output was similar in both conditions argues against such a mechanism, we cannot rule it out completely as acclimatization could have facilitated greater recruitment of alveolar capillaries or increased the pulmonary blood

![Fig. 8. Hemoglobin dissociation curve. Effect of altitude acclimatization on the oxyhemoglobin dissociation curve during maximal exercise after 9–10 wk at 5,260 m (●, fine line) and acute hypoxia (●, thick line). Note the right shift with acclimatization and its impact on \( S_{\text{aO}_2} \) at maximal exercise. (Calculated with mean \( P_{\text{O}_2} \) values corrected for blood temperature and mean \( S_{\text{aO}_2} \) values.)](image-url)
volume during maximal exercise. The higher ventilation attained after acclimatization could have also contributed to attenuate the magnitude of the A-aDO$_2$ since, as shown by West (51), venous admixture and A-aDO$_2$ will fall as a lung with a fixed degree of ventilation-perfusion mismatch is hyperventilated.

Even at SL, intense exercise is associated with some fluid accumulation in the pulmonary interstitial space (7), which is accentuated in AH (10). Thus, part of the A-aDO$_2$ reduction with acclimatization would be explainable if acclimatization results in a lower degree of pulmonary interstitial edema in response to maximal exercise, in severe hypoxia. Pulmonary interstitial edema may amplify A-aDO$_2$ values both by decreasing $D_M$O$_2$ and by enhancing the ventilation-perfusion mismatch (10).

It should be noted that despite the improvement of arterial O$_2$ during exercise after acclimatization, the effect on $S_a$O$_2$ was rather modest (5%) due to the increase in P$_{50}$. Likely the increase of P$_{50}$ facilitates O$_2$ delivery in tissues that cannot use the Bohr effect as efficiently as do the working muscles to facilitate the off-load of O$_2$ from the oxyhemoglobin (29). The higher P$_{50}$ appears not to provide any special advantage as a mechanism to facilitate muscle O$_2$ extraction during maximal exercise after altitude acclimatization as commented on below.

**Muscular O$_2$ Exchange and Diffusing Capacity**

Our data also suggest no deterioration in blood-to-muscle O$_2$ transfer, thus excluding this as a possible factor preventing restoration of VO$_{2\text{max}}$ after altitude acclimatization (Fig. 4F). Fractional O$_2$ extraction across the working legs was not different between AH and CH, and therefore, virtually all of the increase in O$_2$ delivery was reflected in a higher leg VO$_2$. Second, the O$_2$ dissociation curve of the hemoglobin was shifted to the right in CH, as shown by the higher P$_{50}$ values observed after altitude acclimatization. A right-shifted O$_2$ dissociation curve per se facilitates the O$_2$ off-loading from the hemoglobin, especially at the active muscles as it allows Hb desaturation to occur at higher levels of mean capillary Po$_2$ (11, 37). However, in CH, greater hyperventilation and lower Pa$_3$CO$_2$ would tend to move the dissociation curve upward. With a higher mean capillary Po$_2$, the gradient driving the diffusion of O$_2$ from the capillaries to the muscular mitochondria is enhanced and, thus, the diffusion of O$_2$ would be facilitated (45). Calculations of muscle diffusive conductance showed no difference between AH and CH. Thus, this study does not provide any evidence of altered peripheral limitation to the diffusion and/or utilization of O$_2$ after high-altitude acclimatization.

In summary, this study shows that both acute and chronic exposure to severe hypoxia (5,260 m, equivalent to 10.5% inspired O$_2$) reduces maximal cardiac output by a rapidly reversible mechanism related to the level of hypoxia experienced. Despite this similarity in maximal cardiac output, maximal systemic O$_2$ delivery is considerably greater after acclimatization due mainly to an increase in blood [Hb] but also to an improvement of $S_a$O$_2$. As a consequence, after high-altitude acclimatization, systemic O$_2$ delivery reached values that were just 11% below and 54% higher than those observed in normoxia at SL and in AH, respectively. Despite this, VO$_{2\text{max}}$ was only increased by 13% due to reduction in cardiac output and redistribution of blood flow to noncontracting tissues. The reason why the cardiovascular system does not substantially increase O$_2$ delivery to the exercising muscle after altitude acclimatization despite apparently sufficient functional reserve remains unknown.

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