Plasma volume expansion does not increase maximal cardiac output or $\dot{V}O_2_{\text{max}}$ in lowlanders acclimatized to altitude

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Calbet, José A. L., Göran Rådegran, Robert Boushel, Hans Søndergaard, Bengt Saltin, and Peter D. Wagner. Plasma volume expansion does not increase maximal cardiac output or $\dot{V}O_2_{\text{max}}$ in lowlanders acclimatized to altitude. Am J Physiol Heart Circ Physiol 287: H1214–H1224, 2004. First published May 13, 2004; 10.1152/ajpheart.00840.2003.—With altitude acclimatization, blood hemoglobin concentration increases while plasma volume (PV) and maximal cardiac output ($Q_{\text{max}}$) decrease. This investigation aimed to determine whether reduction of $Q_{\text{max}}$ at altitude is due to low circulating blood volume (BV). Eighty Danish lowlanders (3 females, 5 males: age 24.0 ± 0.6 yr, mean ± SE) performed submaximal and maximal exercise on a cycle ergometer after 9 wk at 5,260 m altitude (Mt. Chacaltaya, Bolivia). This was done first with BV resulting from acclimatization (BV = 5.40 ± 0.39 liters) and again 2–4 days later, 1 h after PV expansion with 1 liter of 6% dextran 70 (BV = 6.32 ± 0.34 liters). PV expansion had no effect on $Q_{\text{max}}$, maximal O$_2$ consumption ($VO_2_{\text{max}}$), and exercise capacity. Despite maximal systemic O$_2$ transport being reduced 19% due to hemodilution after PV expansion, whole body $VO_2$ was maintained by greater systemic O$_2$ extraction ($P < 0.05$). Leg blood flow was elevated ($P < 0.05$) in hypervolemic conditions, which compensated for hemodilution resulting in similar leg O$_2$ delivery and leg VO$_2$ during exercise regardless of PV. Pulmonary ventilation, gas exchange, and acid-base balance were essentially unaffected by PV expansion. Sea level $Q_{\text{max}}$ and exercise capacity were restored with hyperoxia at altitude independently of BV. Low BV is not a primary cause for reduction of $Q_{\text{max}}$ at altitude when acclimatized. Furthermore, hemodilution caused by PV expansion at altitude is compensated for by increased systemic O$_2$ extraction with similar peak muscular O$_2$ delivery, such that maximal exercise capacity is unaffected.

however, we have recently shown otherwise, since restoring sea level maximal heart rate at altitude with parasympathetic blockade does not enhance $Q_{\text{max}}$ at altitude (8).

Acclimatization to high altitude entails both a reduction in plasma volume (PV) and a slow increase in red cell mass; consequently, blood volume (BV) remains below sea level values during the first 2–4 mo at altitude (2, 35, 38). Hypovolemia, through its effects on preload, has been proposed as a factor contributing to the reduction of $Q_{\text{max}}$ in chronic hypoxia (1, 2, 37, 48). Experimental evidence for this is, however, not convincing. If the reduction in $Q_{\text{max}}$ is caused by lowered BV, PV expansion should increase $Q_{\text{max}}$ during exercise at altitude and therefore improve maximal O$_2$ uptake ($VO_2_{\text{max}}$) and exercise performance (5, 15, 42).

Accordingly, the aim of this study was to determine whether $Q_{\text{max}}$ can be increased with PV expansion in a group of well-acclimatized lowlanders after 9 wk at an altitude of 5,260 m. Additionally, we assessed the impact of PV expansion on exercise capacity, O$_2$ transport and utilization, gas exchange, and acid-base status during maximal exercise.

METHODS

Subjects. Eight healthy Danish lowlanders (3 women and 5 men) volunteered to participate in these studies. Their mean (± SE) age, height, and weight were 24.0 ± 0.6 yr, 177 ± 3 cm, and 76 ± 4 kg, respectively. All subjects were physically active but none were engaged in regular training. Their main physical activity was biking to move around Copenhagen, and occasionally they participated in recreational sport activities. The subjects were informed about the procedures and risks of the study before giving written informed consent to participate as approved by the Ethical Committee of Copenhagen-Fredriksberg. Euvolemic data from these subjects have been previously reported (13) and are used here as control to the hypervolemic condition.

Experimental design. As part of preliminary examinations, ~2 mo before altitude exposure, subjects performed an incremental exercise test to exhaustion on a cycle ergometer. $VO_2_{\text{max}}$ averaged 56 ± 2 ml·kg$^{-1}$·min$^{-1}$ breathing air at sea level, and peak power output was 300 ± 17 W. This $VO_2_{\text{max}}$ is ~20% higher than reported for the general Danish population of similar age (3) but 20–30% lower than observed in elite endurance athletes.

The present study was conducted at altitude after 9 wk of residence at 5,260 m at Mt. Chacaltaya, Bolivia. During this period, subjects undertook two brief (2–3 days) climbs of neighboring 6,000-m peaks.
After administration of local anesthesia, we inserted Teflon catheters in the femoral artery and vein for blood sampling and for the determination of leg blood flow with the thermodilution technique (4). An additional catheter was placed in a vein in the left forearm for the injection of indocyanine green to measure Q. After catheterization, the subjects rested in the supine position for 30 min before the exercise test.

Exercise protocol. Two exercise levels were undertaken: submaximal (120 W) and maximal exercise, both on a Monark cycle ergometer. Thirty minutes after catheterization, subjects sat on the cycle ergometer and breathed room air (408 mmHg, inspired Po2 (P(I)O2) = 75–76 mmHg) for 5 min before resting measurements were made (Fig. 1). Subjects then cycled at 120 ± 4 W, which was the highest intensity they could tolerate for 10 min when exercising in acute hypoxia (11). Measurements were made at 6 and 10 min. Subsequently, after rest for ~10 min, the maximal exercise test was started with 2 min at the intensity used earlier in the submaximal test. Exercise intensity was then increased rapidly to 90% of previously determined peak levels (maximal power output; Wmax). After 2 min, measurements were made and the load was increased as tolerated to maximal levels by ~20–40 W every minute until reaching the maximal exercise intensity. After ~1 min at the maximal load, measurements were repeated. Then, if subjects were not exhausted, the load was increased by 20 W and measurements were repeated after 1 min and so on until the subjects were almost exhausted. Still cycling at this workload, subjects were switched to 55% O2 in nitrogen (P(O)2 of ~200 mmHg), and, after 2 min at this P(O)2, a further set of measurements was made. Finally, the workload was increased as tolerated at a rate of 20 W/min to a new maximal value, with measurements repeated.

Measurements. BV was determined with indocyanine green (Akorn) while the subjects rested quietly in the supine position (21). Pulmonary O2 consumption (V(O)2), CO2 production (V(CO2)), and expired minute ventilation (V(E)) were measured continuously with an online system (Medical Graphics CPX, Minneapolis, MN) and averaged every 15 s. During the incremental exercise, the highest V(O)2 value recorded during any single 15-s interval was taken as the V(O)2 max. At peak effort, the measurements were made when the V(O)2 had plateaued and the subjects were close to exhaustion. Femoral venous blood flow (i.e., leg blood flow; LBF) was measured in the femoral vein by constant-infusion thermodilution as described in detail elsewhere (4). Arterial blood pressure was monitored continuously by a disposable transducer (model T100209A, Baxter). The blood pressure transducer and the electrocardiogram electrodes were interfaced with a monitor, which was in turn connected to the data acquisition system. Q was measured with the dye-dilution method with the use of indocyanine green as previously reported (8, 10, 11, 13, 20, 39). Blood [Hb] and O2 saturation (SO2) were measured with a cooximeter (OSM 3 Hemoximeter, Radiometer), P02, Pco2, and pH were determined with a blood gas analyzer (ABL 5, Radiometer) and corrected for measured femoral vein blood temperature (45). Hematocrit was determined by microcentrifugation on triplicate samples. Plasma K+ concentration was measured with an electrolyte metabolite analyzer (EML 105, Radiometer). Plasma norepinephrine and epinephrine concentrations were measured by HPLC with electrochemical detection (22).

Calculations. Arteriovenous O2 concentration difference [(a-v)O2] was calculated from the difference in femoral arterial and femoral venous O2 concentrations. This difference was then divided by arterial concentration to give O2 extraction. O2 delivery was computed as the product of blood flow and CaO2. Leg VO2 was calculated as the product of LBF and the (a-v)O2. Non-LBF was computed as the difference between Q and 2-leg blood flow (2-LBF). Mean blood pressure was obtained by integrating the blood pressure curve over time. Systemic and leg vascular conductances were calculated as blood flow (either LBF or Q) divided by mean arterial pressure.

Statistical analysis. Differences in the measured variables among conditions and exercise levels were analyzed with two-way ANOVA for repeated measures, with [Hb] and exercise intensity as within-subjects factors. Two separated ANOVA analyses were performed: one for the part of the experiment where subjects breathed room air and another for the exercise with hypoxia breathing. When F was significant in the ANOVA, planned pairwise specific comparisons were carried out using Student’s paired t-test adjusted for multiple comparisons with the Bonferroni procedure. The influence of hypoxia on variables measured at maximal exercise was tested by use of the Student’s paired t-test. Comparisons between maximal exercise in normoxia (sea level control experiments) and chronic hypoxia were analyzed.
also performed using the Student’s paired t-test. In addition, the mean blood flow response during the euvolemic conditions was compared with the mean LBF observed during the hypervolemic conditions, also by use of a Student’s paired t-test. Simple linear regression analysis was performed to determine linear relations between variables. Significance was accepted at P < 0.05. Data are reported as means + SE.

RESULTS

Exercise capacity and VO2. Breathing ambient air at maximal exercise, subjects showed no significant differences in maximal pulmonary or leg VO2 or in power output comparing euvolemic and hypervolemic conditions (Fig. 2, A and B). When 55% O2 was breathed, maximal power output and leg VO2 were increased, attaining exhaustion values similar to those observed at sea level.

Pulmonary ventilation and gas exchange. During submaximal exercise under conditions of breathing room air, a similar pulmonary ventilation, VCO2, and ventilatory equivalents for O2 and CO2 (VE/V02 and VE/VCO2, respectively) were observed before and after PV expansion (Fig. 3, A–D). As depicted in Fig. 3E, alveolar PO2 (PaO2) was slightly higher during maximal exercise after PV expansion than before (61 ± 2 and 63 ± 1 mmHg, P < 0.05), likely linked to an increased pulmonary ventilation after PV expansion (162 ± 14 and 169 ± 15 l/min, P = 0.05). Before PV expansion, the alveolar–arterial PO2 gradient [(A-a)DO2] was 13.4 ± 0.6 and 15.8 ± 1.1 mmHg during submaximal and maximal exercise, respectively, and was increased to 14.8 ± 0.8 and 17.2 ± 0.9 mmHg after PV expansion (P < 0.05) (Fig. 3F). Pulmonary ventilation, VCO2, VE/V02, VE/VCO2, PaO2, and (A-a)DO2 increased with exercise intensity (P < 0.05).

[Hb] and arterial and femoral venous blood gases. The 9 wk of exposure to altitude increased blood [Hb] by 36% compared with that at sea level (185 ± 4 vs. 136 ± 5 g/l, averaging arterial and venous data), whereas PV expansion caused a 19% drop in [Hb] due to hemodilution (Table 1). Arterial PO2 (PaO2), PCO2, and SO2 were all reduced as expected at altitude, but PV expansion had no significant effect on these variables at rest or at any exercise level (Table 1). O2 extraction, defined as (a-v)O2 divided by arterial O2 concentration, increased as a response to the reduction in [Hb] caused by the PV expansion (Fig. 4, A and B). Systemic O2 extraction increased with exercise intensity (P < 0.05). This increase was more accentuated after hemodilution than during the euvolemic condition, as indicated by the significant interaction in the ANOVA analysis.

Q, LBF, and arterial O2 delivery. Resting Q was increased by 34% (P < 0.05) with PV expansion and heart rate by 35% (P < 0.05), which implies that, at rest, stroke volume was similar in both conditions. As previously reported, resting stroke volume at altitude was, however, 24% lower than at sea level (10). As illustrated in Figs. 5 and 6, Q, 2-LBF, systemic O2 delivery, leg O2 delivery, heart rate, and stroke volume increased with exercise intensity. There was a significant interaction in the Q response to exercise while the subjects breathed room air. At maximal exercise under conditions of breathing ambient air, Q was the same at both levels of BV (Fig. 5A). However, during submaximal exercise in the expanded volume condition, Q was elevated because of an enhancement of heart rate (Fig. 6A, P < 0.05), since the stroke volume response was not affected by PV expansion at any exercise intensity regardless of oxygenation status (Fig. 6B). In contrast, when all leg flow data were pooled together, LBF was higher during the volume-expanded condition at any work rate (Fig. 5B) (P = 0.05). During maximal exercise in chronic hypoxia, PV expansion resulted in ~10% higher “double product” (heart rate times systolic blood pressure) compared with the euvolemic condition (P < 0.05).

Fig. 2. Pulmonary O2 uptake (VO2) (A) and 2-leg VO2 (B) during submaximal and maximal exercise, with the blood volume (BV) attained after 9 wk of residence at an altitude of 5,260 m or euvolemia and after hypervolemic hemodilution. Exercises performed while room air was breathed at altitude (hypoxia) are represented by solid symbols. Hyperoxic conditions at altitude [inspired O2 fraction (FiO2) = 0.55] are represented by open symbols. Because of technical constraints, pulmonary VO2 was not measured during hypoxia at altitude; instead, the values observed during the sea level control experiments are plotted (○). Sea level data were obtained in the same subjects using the same experimental protocol at least 6 mo after the return to sea level, as recently reported (12). §P < 0.05, comparison between hypoxia and hypervoxia at the same exercise intensity and Hb concentration ([Hb]); ¶P < 0.05, difference between maximal exercise in hypoxia and maximal exercise in hypervoxia at the same [Hb]; and ¥P < 0.05, compared with maximal exercise in normoxia at sea level.
Systemic O₂ delivery was reduced after PV expansion at all exercise intensities and inspired O₂ fractions (F İ O₂) with the exception of submaximal exercise, for which similar values were observed at the two levels of volemia tested (Fig. 5C). Despite the lower CaO₂ in the hypervolemic condition, leg O₂ delivery was maintained because of the increase in LBF (Fig. 5D). Taken together with the above-mentioned increases in O₂ extraction, these data account for the lack of effect of PV expansion on V˙O₂ at either whole body or leg level.

**Distribution of Q.** During maximal exercise, Q was unaffected by PV expansion, and a nonsignificant increase of peak LBF (P = 0.10) combined with a nonsignificant reduction of perfusion of the body [6.2 ± 0.2 l/min (euvolemia) vs. 4.6 ± 1.1 l/min (hypervolemia); P = 0.07] was observed. In addition, non-LBF during maximal exercise increased with hyperoxic breathing (ANOVA, P < 0.05). This effect was significant only in the euvolemic condition, where non-LBF increased from 6.2 ± 0.7 to 8.4 ± 1.1 l/min (P < 0.05), and non-LBF was similar during the hypervolemic condition (4.6 ± 1.1 to 6.0 ± 1.2 l/min, breathing room air and hyperoxia, respectively; P = 0.2). At maximal exercise with hyperoxia, non-LBF was greater in the euvolemic than in the hypervolemic condition (P < 0.05).

**Mean arterial pressure, systemic vascular conductance, and leg vascular conductance.** Vascular conductances increased with exercise intensity (P < 0.05). During submaximal and maximal exercise, mean arterial pressure and total systemic vascular conductance were similar regardless of BV and F İ O₂ (Figs. 7A and 4B). Leg vascular conductance, however, was increased by PV expansion (P < 0.05) (Fig. 7C).
**Table 1. Femoral arterial and venous blood gases and acid-base balance**

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<tr>
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<th>Rest</th>
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<td><strong>BE, mmol/l</strong></td>
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<td><strong>CO2, ml/l</strong></td>
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<td><strong>CaO2, ml/l</strong></td>
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*Values are means ± SE. Femoral arterial and venous blood gases and acid-base balance at rest and during submaximal and maximal exercise after high-altitude acclimatization with the circulating blood volume attained after 9 wk of residence at an altitude of 5,260 m (euvolemia; Euv) and after plasma volume (PV) expansion (PVE).* All venous data reflect femoral venous samples. Hyp, hypoxia; PO2; A, arterial; V, venous; Pao2, arterial partial pressure of O2; PVo2, venous PO2; S02, arterial O2 saturation; SvO2, venous O2 saturation; CaO2, arterial O2 content; CVo2, venous O2 content; Pao2, arterial partial pressure of CO2; PCvo2, venous partial pressure of CO2; BE, base excess. *P < 0.05 compared with control condition (Euv) after altitude acclimatization; †P < 0.05 compared with same condition while breathing room air at altitudes and ‡P < 0.05 compared with maximal exercise while breathing room air.

**Catecholamines.** As depicted in Fig. 8, both catecholamines increased with exercise intensity (P < 0.05). PV expansion did not affect the arterial epinephrine and norepinephrine responses at any work rate or FIO2, but both hormones reached a higher concentration during maximal exercise with hyperoxia than at maximal exercise while breathing room air (Fig. 8) (P < 0.05). Q was closely related to the arterial epinephrine (r = 0.86, P < 0.01) and norepinephrine (r = 0.94, P < 0.01) concentrations across experimental conditions.

**DISCUSSION**

The main finding of this study is that expansion of PV with 1 liter of 6% dextran in humans well acclimatized to a very high altitude had no effect on Qmax and VO2max. Thus this study does not support the hypothesis of Alexander et al. (2) that PV expansion immediately before exercise should enlarge Qmax, VO2max, or maximal power output.

**Effect of PV expansion on Q at rest and during submaximal exercise.** The fact that our subjects remained active, hiking around the laboratory facilities and participating in two short expeditions (2–4 days) to peaks at 6,080 and 6,500 m, could have contributed to preserve exercise capacity and, perhaps, to mitigate the expected drop in PV with chronic hypoxia (44). However, compared with normoxic sea level values, resting stroke volume was markedly reduced after 9 wk at 5,260 m. The reduction in resting stroke volume at altitude is a well known phenomenon, which has been attributed to decreased preload in chronic hypoxia (1, 2, 37, 48). This explanation is supported by the observation of reductions in left ventricle end-diastolic diameter, cardiac filling pressures, and circulating values of PV volume in the 3–5 liters at sea level.
BV after altitude acclimatization (1, 2, 37, 48). The BV after 9 wk at 5,260 m was 10–15% lower than expected for physically active subjects (29, 44, 51). Thus a lower circulating BV and hence preload could account for the reduced resting stroke volume after altitude acclimatization in our subjects. PV expansion effectively increased resting (+34%) (10) and submaximal exercise $Q$ (+12%), meaning that venous return was elevated by PV expansion. For a fixed heart rate, inotropic state, and afterload, an increased venous return elicits an enhancement of stroke volume because of the recruitment of the Frank-Starling mechanism. In the present investigation, however, the enhancement of resting and submaximal $Q$ was entirely achieved through the elevation of heart rate, perhaps facilitated by the so-called Bainbridge reflex (27). Parallel experiments performed during this expedition have demonstrated a paradoxical high activity of both the parasympathetic (8) and sympathetic (10, 23) branches of the autonomous nervous system at rest and during submaximal and maximal exercise.

**Fig. 5.** Cardiac output ($Q$) (A), 2-leg blood flow (2-LBF) (B), systemic $O_2$ delivery (C), and 2-leg $O_2$ delivery (D) during submaximal and maximal exercise, with the BV attained after 9 wk of residence at an altitude of 5,260 m or euvalmia and after PVE. Exercises performed while room air was breathed at altitude (hypoxia) are represented by solid symbols. Hyperoxic conditions at altitude (FiO$_2$ = 0.55) are represented by open symbols. *$P < 0.05$, comparison between euvalmia and PVE; §$P < 0.05$, comparison between hypoxia and hyperoxia at the same exercise intensity and [Hb]; and ¶$P < 0.05$, difference between maximal exercise in hypoxia and maximal exercise in hyperoxia at the same [Hb].

**Fig. 6.** Heart rate (A) and stroke volume (B) during submaximal and maximal exercise, with the BV attained after 9 wk of residence at an altitude of 5,260 m or euvalmia and after PVE. Exercises performed while room air was breathed at altitude (hypoxia) are represented by solid symbols. Hyperoxic conditions at altitude (FiO$_2$ = 0.55) are represented by open symbols. *$P < 0.05$, comparison between hypoxia and hyperoxia at the same exercise intensity and [Hb]; and ¶$P < 0.05$, difference between maximal exercise in hypoxia and maximal exercise in hyperoxia at the same [Hb].
exercise as well. Given the fact that sympathetic activity was slightly decreased by PV expansion (23), it is likely that the mechanism accounting for the increase in resting and submaximal exercise heart rate involves an attenuation of parasympathetic activity.

Effect of PV expansion on $Q_{\text{max}}$ and $V_{\text{O}_2\text{max}}$. The absence of enhancement of $Q_{\text{max}}$, despite a substantial increase of PV, suggests that the level of hemoconcentration existing after 9 wk at altitude has little if any influence on cardiac function during maximal exercise at altitude, as recently demonstrated (13). Like us, Alexander et al. (2) found greater $Q_{\text{max}}$ values during submaximal exercise after PV expansion. However, the effect of PV expansion on stroke volume was not conclusive, since the increase in $Q_{\text{max}}$ was brought about through an enhancement of heart rate in one subject, whereas the other subject increased the stroke volume (2). The present investigation shows that after acclimatization to high altitude, the increase in submaximal $Q_{\text{max}}$ after PV expansion is brought about by an enhancement of the chronotropic response while stroke volume is maintained.

In contrast to our results, a small expansion of PV (220 ml) has been reported to increase $V_{\text{O}_2\text{max}}$ by 9% in subjects acclimatized for 1 wk to 4,350 m, followed by 10–12 days at a simulated altitude of 6,000 m (40). Although the subjects studied by Robach et al. (40) exhibited a 26% reduction in PV after 10–12 days at 6,000 m (compared with sea level), it does not seem plausible that the small PV expansion induced in their study by the administration of 220 ml of 6% hydroxyethyl starch could have accounted for the enhancement of $V_{\text{O}_2\text{max}}$ on the basis of an elevation of the circulatory volume as they argued. Given the tight coupling that exists between $O_2$ supply and $V_{\text{O}_2}$ at maximal exercise, particularly in hypoxia (11, 12, 39), $Q_{\text{max}}$ and/or leg blood flow would have had to be enhanced by >9% (due to the hemodilutional effect of PV expansion) to achieve a 9% higher $O_2$ delivery at peak exercise. Robach et al. did not measure, however, $Q_{\text{max}}$ nor muscular $O_2$ delivery, and thus they could not explain the mechanisms by which $V_{\text{O}_2\text{max}}$ was improved under their experimental conditions. Part of the discrepancy between our findings and those of Robach et al. may be ascribed to the fact that the experiments of Robach et al. were carried out after 3 wk of hypoxia exposure, a period during which BV is likely lower than after 9 wk of acclimatization.

In agreement with our results, Young et al. (54) did not find any significant effect of 700 ml of autologous erythrocyte infusion, performed 24 h before the ascent to Pike’s Peak (4,300 m), on the $V_{\text{O}_2\text{max}}$ response 24 h and 9 days after the ascension. The fact that $V_{\text{O}_2\text{max}}$ was not increased with the erythrocyte transfusion in the experiments of Young et al. together with the observation made in the present investigation of no deterioration of $V_{\text{O}_2\text{max}}$ with hypervolemic hemodilution indicates that different mechanisms limit $V_{\text{O}_2\text{max}}$ during exercise in acute and chronic hypoxia (11, 12).

Other investigations on the effects of PV expansion on $Q_{\text{max}}$ have been limited to sea level conditions. In the present study, sea level-equivalent oxygenation was reproduced by allowing the subjects to breathe a hypoxic ($F_{\text{O}_2} = 0.55$) gas mixture at altitude. This resulted in similar increases of $Q_{\text{max}}$ in both normal and expanded PV conditions. Moreover, with hyperoxia $Q_{\text{max}}$ at altitude increased to the same values as at sea level (11, 12). Had the reduction in $Q_{\text{max}}$ been caused by hypovolemia and

![Image](http://apjheart.physiology.org/)

**Fig. 7.** Mean arterial pressure (MAP, A), systemic vascular conductance (Sys VC, B) and 1-leg vascular conductance (LVVC, C) during submaximal and maximal exercise, with the BV attained after 9 wk of residence at an altitude of 5,260 m or euvolemia and after hypervolemic hemodilution (PVE). Experiments performed while room air was breathed at altitude (hypoxia) are represented by solid symbols. Hypoxic conditions at altitude ($F_{\text{O}_2} = 0.55$) are represented by open symbols. *$P < 0.05$, comparison between euvolemia and PVE; and ¶$P < 0.05$, difference between maximal exercise in hypoxia and maximal exercise in hyperoxia at the same [Hb].
lowered preload, hyperoxia would not have led to such increases. In general, previous investigations have reported no increase of $Q_{\text{max}}$ during exercise at sea level with PV expansion (16, 26, 41, 49, 51). Robinson et al. (41) and Ekblom et al. (16) did not report any significant change in $Q_{\text{max}}$ after an autologous transfusion of 0.8–1.2 liters of blood. Kanstrup and Ekblom (26) observed a nonstatistically significant increase of $Q_{\text{max}}$ of 2 l/min after inducing a PV expansion of 700 ml. In contrast, two other studies have reported an increase of $Q_{\text{max}}$ with blood transfusion (49) and PV expansion (51). Thomson et al. (49) found an increase of 2.5 l/min after an autologous blood transfusion of 1 liter in four subjects. However, in the later study, $Q$ at peak exercise was estimated from the submaximal relationship between $Q$ and $V_O_2$, which may raise some concerns about the validity of these findings (49). PV expansion with 500 ml of 6% dextran resulted in 3% greater $Q_{\text{max}}$, measured with the acetylene rebreathing technique in nine elite cyclists (51). Several factors have been proposed to account for these discrepancies between studies. It has been suggested that subjects with a lower degree of fitness (lower $V_O_2_{\text{max}}$) and lower $V_O_2$ before expansion are more prone to experience an elevation of $Q_{\text{max}}$ with PV expansion (29, 51). Despite our subjects having $V_O_2_{\text{max}}$ values that were ~20% higher than those reported for the general Danish population of similar age (3), but 20–30% lower than elite endurance athletes (44, 51), no enhancement of $Q$ was observed with PV expansion in any condition.

Why did $Q_{\text{max}}$ not increase with PV expansion at altitude? PV expansion could fail to increase preload if left ventricle distension is limited by other factors such as some degree of pericardial constraint (47) and increased right ventricular volume due to high afterload on the right side of the heart, caused by pulmonary hypertension (48). Even at higher altitudes (and degree of hypoxia) than in the present expedition, only a mild (not quantified) right ventricle dilation has been reported (48), which was not accompanied by any sign of right heart failure. If present at all, any sign of right heart failure should have been really mild and transitory, because hyperoxia at altitude restored sea level $Q_{\text{max}}$ in both volmic conditions. Thus it appears unlikely that these changes could really occur in healthy subjects during acclimatization to 5,260 m; indeed, severe damage should be inflicted to the right ventricle to cause right cardiac failure (19).

Other factors such as increased afterload and attenuated myocardial contractility could have been responsible for the low $Q_{\text{max}}$ after altitude acclimatization. Chronic hypoxia may decrease myocardial contractility because of an alteration of intracellular $Ca^{2+}$ concentration ([Ca$^{2+}$]$_i$) homeostasis, such that the magnitude of the [Ca$^{2+}$]$_i$ transient in response to several inotropic factors is attenuated (33, 34, 46). Chronic hypoxia ($F_iO_2 = 0.10$) is associated with reduced expression of and $Ca^{2+}$ uptake by sarco(endo)plasmic reticulum $Ca^{2+}$-ATPase (SERCA), reduced release of $Ca^{2+}$ via ryanodine receptors, and reduced extrusion of $Ca^{2+}$ by $Na^+/Ca^{2+}$ exchange in rats (32). Although we cannot rule out a reduced myocardial contractility after altitude acclimatization, the fact that our subjects were able to reach at altitude the sea level $Q_{\text{max}}$ just by breathing a hyperoxic gas at altitude (10, 13) argues against any important impairment of myocardial contractility elicited by structural changes in the cardiomyocytes. Moreover, myocardial contractility appears to be preserved in humans submitted to higher levels of chronic hypoxia (37).

The aerobic demand of the heart may be estimated by calculating the double product (the product of heart rate times systolic arterial pressure) (25, 28). Maximal exercise double product has been reported to be lower in hypoxia than in normoxia (9), moderate hyperoxia (8), or pure hyperoxia (48). The present investigation shows that the double product is significantly increased by PV expansion during maximal exercise in chronic hypoxia. The latter implies that at the moment of exhaustion in the euvoletic condition, the heart was still able to further increase its work, despite the fact that with hypervolemia $PaO_2$ was similar while $CaO_2$ was lower than during euvoletic. Perhaps after PV expansion, the work efficiency of the heart improved because of additional recruitment of the Frank-Starling mechanism. However, the lack of enhancement of stroke volume at maximal exercise with PV expansion argues against this possibility in our experimental conditions. Alternatively, the increase of maximal double product with PV expansion could have been brought about by rising coronary blood flow and hence coronary $O_2$ delivery.
Blood viscosity increases exponentially with hematocrit, and consequently afterload may be greater at altitude acclimatization, impairing systolic emptying. PV expansion was, however, accompanied by 19% hemodilution without any significant effect on mean arterial pressure, suggesting that the level of hemococoncentration reached after altitude acclimatization could have exerted only a marginal influence on the afterload during maximal exercise. Furthermore, when hypoxia was eliminated acutely in the euvolemic as well as in the hypervolemic conditions by breathing 55% O₂, the maximal heart rate, stroke volume, and Q observed at altitude were similar to those obtained subsequently in the same subjects at sea level (11). The increase in Q with hypoxia at altitude occurred despite mean arterial pressure remaining at the same level, i.e., with the same afterload, a greater Q_{max} was achieved just by improving oxygenation. Had afterload been the limiting factor of Q_{max} at altitude, such an increase should not have been seen.

Effect of hemodilution on leg blood flow and vascular conductance. PV expansion caused hemodilution, but maximal leg O₂ delivery and leg VO₂ were maintained at the euvolemic level. The latter was possible because, after PV expansion, maximal leg blood flow at altitude tends to be higher, whereas the perfusion to vascular beds apart from the legs is reduced. These changes are similar but of lower magnitude than observed in the same subjects with a greater level of hemodilution (13). Our results suggest that the elevation of leg blood flow with hypervolemic hemodilution was brought about by increasing leg vascular conductance, as observed during isovolemic hemodilution (13), inasmuch as perfusion pressure was not altered by hypervolemia. The increase of maximal leg vascular conductance occurred despite similar arterial catecholamine concentrations in both conditions, suggesting comparable sympathetic vasoconstrictor tone. However, for a given norepinephrine clearance, the arterial norepinephrine concentration may remain unchanged and leg sympathetic tone decreased if norepinephrine spillover is reduced across the legs and at the same time increased in other vascular beds. Maximal leg vascular conductance could have also been increased through enhanced vasodilating activity, probably of metabolic origin (24, 43).

Effect of hemodilution on O₂ transport and utilization. Previous investigations in which [Hb] was isovolemically reduced in polycytemic highlanders (52) or lowlanders acclimatized to altitude (13) showed no reduction of maximal exercise capacity or VO₂_{max}. The current study also demonstrates that maximal exercise capacity and VO₂_{max} are maintained after hypervolemic hemodilution. Borst et al. (7) reported marked improvements in pulmonary hemodynamics and gas exchange with hemodilution in patients with severe chronic obstructive pulmonary disease. In contrast, this study shows that pulmonary ventilation, gas exchange, and acid-base balance are essentially not affected by hypervolemic hemodilution in healthy humans exercising at altitude.

Potential limitations. The fact that hypervolemic exercise was preceded by another experiment (isovolemic hemodilution) (13) might have influenced some of the results here reported. However, the 90-min resting period that followed the isovolemic hemodilution experiments should have minimized their impact on the subsequent hypervolemic experiments. In fact, the subjects were able to reach sea level Q_{max} during the hypervolemic conditions with hyperoxia. The population here studied has some particularities that should be taken into consideration. First, our subjects had an enhanced VO₂_{max} compared with young adults of the general Danish population (3). It has been suggested that because trained subjects have increased BV, they may be less responsive to PV expansion during exercise at sea level (51). Despite this fact, our subjects were quite sensitive to PV expansion as reflected by the substantial elevation of resting and submaximal exercise Q after PV expansion at altitude. Thus it seems that our findings cannot be attributed to a high VO₂_{max} of our subjects. Second, the study population included three women; this fact could have caused some heterogeneity in the ventilatory and cardiovascular responses to altitude acclimatization. However, our data and that of others (6, 17, 18, 30, 31, 53) show that the acclimatization process to altitude is rather similar in male and females, with the exception of the known increased ventilation that women have at both sea level and altitude. The latter has a minor impact on pulmonary gas exchange in hypoxia, i.e., the SaO₂ and PaO₂ are almost the same in males and females subjected to chronic hypoxia (6, 17, 18, 30, 31, 53). Third, the high between-subject variability might have increased the risk for a type II error due to insufficient statistical power.

In summary, this study has shown that a reduced circulating BV is not a primary factor in explaining the reduction in Q_{max} observed after altitude acclimatization. Substantial acute PV expansion by ~1 liter at altitude has no effect on Q_{max}, VO₂_{max}, or exercise capacity in well-acclimatized lowlanders. Overall, leg blood flow in the working legs was enhanced after PV expansion and compensated entirely for the dilutional decrease in [Hb] resulting in similar O₂ delivery and leg VO₂ at maximal exercise in both conditions. Despite maximal systemic O₂ transport being reduced because of 19% hemodilution, VO₂_{max} was maintained by greater systemic O₂ extraction after PV expansion. Under conditions of both normal and increased BV, when the sea level environment was reproduced by the utilization of hyperoxia at altitude, Q_{max} and work rate increased to values similar to sea level. This further supports our finding that Q_{max} at altitude is not limited by a lower circulating volume or increased blood viscosity.

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