Role of the autonomic nervous system in the reduced maximal cardiac output at altitude

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Role of the autonomic nervous system in the reduced maximal cardiac output at altitude. J Appl Physiol 93: 271–279, 2002; 10.1152/japplphysiol.00323.2001.—After acclimatization to high altitude, maximal exercise cardiac output (Q˙T) is reduced. Possible contributing factors include 1) blood volume depletion, 2) increased blood viscosity, 3) myocardial hypoxia, 4) altered autonomic nervous system (ANS) function affecting maximal heart rate (HR), and 5) reduced flow demand from reduced muscle work capability. We tested the role of the ANS reduction of HR in this phenomenon in five normal subjects by separately blocking the sympathetic and parasympathetic arms of the ANS during maximal exercise after 2-wk acclimatization at 3,800 m to alter maximal HR. We used intravenous doses of 8.0 mg of propranolol and 0.8 mg of glycopyrrolate, respectively. At altitude, peak HR was 170 ± 6 beats/min, reduced from 186 ± 3 beats/min (P = 0.012) at sea level. Propranolol further reduced peak HR to 139 ± 2 beats/min (P = 0.001), whereas glycopyrrolate increased peak HR to 184 ± 3 beats/min, confirming adequate dosing with each drug. In contrast, peak O2 consumption, work rate, and Q˙T were similar at altitude under all drug treatments [peak Q˙T = 16.2 ± 1.2 (control), 15.5 ± 1.3 (propranolol), and 16.2 ± 1.1 l/min (glycopyrrolate)]. All Q˙T results at altitude were lower than those at sea level (20.0 ± 1.8 l/min in air). Therefore, this study suggests that, whereas the ANS may affect HR at altitude, peak Q˙T is unaffected by ANS blockade. We conclude that the effect of altered ANS function on HR is not the cause of the reduced maximal Q˙T at altitude.

altitude acclimatization; maximal exercise; autonomous nervous system; heart rate; propranolol; glycopyrrolate; oxygen uptake; acetylene uptake

WHEN A NORMAL SUBJECT exercises while breathing air at sea level (SL), heart rate (HR) and cardiac output (Q˙T) rise linearly in proportion to work rate (38) until maximal exercise and maximal O2 consumption (V˙O2 max) are reached. When the same subject ascends rapidly to altitude, V˙O2 max is reduced but maximal HR and Q˙T are both similar to results at SL (46) or are slightly reduced (8, 26, 42). When the same subject remains at this altitude for 2 wk or more, acclimatization occurs with increases in ventilation, hemoglobin (Hb) concentration, and renal excretion of bicarbonate and water. However, V˙O2 max is not altered over 2 wk at such altitudes, whereas maximal Q˙T clearly decreases (1, 32, 43), implying an increase in arterial O2 concentration, an increase in peripheral O2 extraction, or both. This independence of V˙O2 max from Q˙T does not prove that Q˙T per se has no effect on maximal exercise capacity at altitude. In fact, because a high Q˙T is generally considered to be a key factor enabling high exercise levels (6), the reduction in maximal Q˙T on acclimatization has the potential for limiting V˙O2 max at altitude. Thus V˙O2 max might have been higher after acclimatization had peak Q˙T not fallen.

Several hypotheses have been put forward to explain the acclimatization-induced reduction in maximal Q˙T (reviewed in Ref. 45). First, water shifting out of the vascular space, together with fluid loss through greater sweating, respiration, and urine production with altitude, leads to reduced plasma volume, which, when not compensated for by an increase in erythrocyte volume, leads to a reduced blood volume. This in turn could lead to lower cardiac filling pressures (preload), compromising maximal Q˙T and V˙O2 max (37). Second, increased Hb concentration due to enhanced renal erythropoietin release and plasma volume loss elevates blood viscosity, which could reduce maximal Q˙T. Third, myocardial contractility could be directly reduced by the hypoxia of altitude. Fourth, maximal Q˙T might be reduced by adaptations in the autonomic nervous system (ANS), affecting HR in the absence of compensatory changes in stroke volume. A fifth more or less “passive” hypothesis states that none of the above pathophysiological mechanisms is responsible and that the reduced maximal Q˙T is simply the result of a low maximal work rate and V˙O2 max. Accordingly, the skeletal muscle at altitude has a reduced ability to work because of the reduced PO2, and, because Q˙T is closely correlated with O2 uptake (V˙O2), maximal Q˙T is reduced.

The present study was undertaken to investigate the fourth hypothesis, i.e., the role of the ANS. As has been shown previously, acclimatized humans and rats both show evidence of cardiac β-receptor desensitization. 

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(21, 33, 34) and increased muscarinic receptor activity (22), which could provide the basis for a role of the ANS in this phenomenon. With the use of pharmacological interventions to block either arm (sympathetic and parasympathetic) of the ANS, clear effects have been shown on maximal HR (reduction with propranolol and increase with atropine), whereas peak exercise capacity and $\dot{V}O_2$ were unchanged (14, 29). As of yet, no studies with these interventions have been performed in which maximal $Q_T$ at SL and after acclimatization were compared. We hypothesized that, despite evidence of altered ANS function after altitude acclimatization with attendant effects on HR, these alterations are not the cause of the reduced maximal exercise $Q_T$. We used sympathetic and parasympathetic blockade (separately) before and after altitude acclimatization to determine whether maximal $Q_T$ was sensitive to the ANS state. In this paper, we report that, after altitude acclimatization, such blockade predictably altered maximal HR but had no significant effects on maximal $Q_T$, $\dot{V}O_2$, or work rate.

METHODS

Subjects. The Human Subjects Committee of the University of California (San Diego, CA) approved this study. Six (5 men, 1 woman) healthy nonsmoking subjects were included in the study. They were all physically active, but not competitive athletes, and had no prior history of respiratory disease, cardiac disease, or high-altitude pulmonary or cerebral edema. After subjects gave written, informed consent, a history was obtained and a physical examination was performed to exclude cardiopulmonary abnormalities. All subjects were then screened for pulmonary disease by standard spirometry. Subject characteristics are summarized in Table 1.

Study design. After a standard progressive maximal cycle exercise test at SL to determine peak $\dot{V}O_2$ and workload, noninvasive measurements were made of $Q_T$ and HR at five different levels of exercise: rest, at 30, 60, and 90% of SL, and at 100% of SL maximum. All measurements were made over the course of 12 such exercise bouts spaced out over 6 experimental days, at 2 bouts per day. On the first 3 days, measurements were made at SL in San Diego. After a 2-wk acclimatization period (WM) at the White Mountain Research Station (Barcroft Station, Face Laboratory), near Bishop, California, where the altitude is 12,470 feet (3,800 m) and barometric pressure is ~482–486 mmHg, another 3 days of measurements were carried out. On each experimental day, subjects received 1) no drug (control), 2) sympathetic blockade with propranolol, or 3) parasympathetic blockade with glycopyrrolate. On each day, two exercise tests were performed, one with subjects breathing ambient air [inspiratory fraction of $O_2 (FIO_2) = 0.209$] and one with subjects breathing a gas mixture with an $FIO_2$ of 0.125 at SL or 0.34 at WM. In this way, it was ensured that there were comparable high and low inspired $P_{O_2}$ ($P_{O_2i}$) (further referred to as normoxia and hypoxia, respectively) at both locations. The order of sessions was chosen at random. On a day with sympathetic blockade, 6 mg of propranolol were administered intravenously before the first exercise bout. After this bout and a 1-h resting period, another 2 mg of the drug were administered before the second bout. On a day with parasympathetic blockade, 0.8 mg of glycopyrrolate was administered intravenously before the first bout and another 0.2 mg before the second. All drug administrations and exercise tests were performed under close and continuous electrocardiogram (ECG) and blood pressure monitoring. At both SL and WM, at least 24 h were allowed between any 2 experimental days to ensure washout of propranolol and glycopyrrolate. On the control (no drug) day at SL only, a 20-gauge radial artery cannula was inserted to allow comparison of arterial $O_2$ saturation ($S_aO_2$) by cooximetry and by noninvasive pulse oximetry. These comparisons are not germane to the present study and are reported elsewhere (48).

$Q_T$ measured by short-term acetylene uptake. $Q_T$ was measured in all subjects by a nonrebreathing acetylene ($C_2H_2$) technique, based on the principles of mass balance. The method, described previously in detail, has been validated in healthy subjects up to maximal exercise (3). In short, it relies on the fact that the rate of alveolar absorption of a gas soluble in blood, such as $C_2H_2$, is proportional to pulmonary blood flow. A subject breathes from a bag containing 1% $C_2H_2$ and 5% helium for 20 breaths. Bag $P_{O_2}$ is similar to that inspired during the particular exercise run. This is a nonrebreathing method that therefore does not change $P_{O_2}$ or $P_{CO_2}$ during its application. $Q_T$ is calculated with a computer algorithm by using minute ventilation, inspired $C_2H_2$ concentration, helium-corrected end-tidal $C_2H_2$ concentration, end-tidal $P_{CO_2}$, mixed expiratory $P_{CO_2}$, and the blood-gas partition coefficient of $C_2H_2$ measured at rest and during exercise on each experimental day, as reported by Barker et al. (3).

Exercise and $\dot{V}O_2$. All exercise tests were performed on an electronically braked cycle ergometer (Excalibur, Quinton Instruments, Groningen, The Netherlands), with HR monitored by a cardiac monitor (Lifepak 6, Physio-control, Redmond, WA). Subjects breathed through a nonrebreathing valve (model 2700, Hans Rudolph, Kansas City, MO), with a dead space of 100 ml. Mixed expired gas was sampled continuously from a heated mixing chamber, and concentrations of $O_2$ and $CO_2$ were measured by mass spectrometry (model 1100, Perkin-Elmer, Pomona, CA). Expired gas flow was measured with a pneumotach (no. 3 Fleisch) and a differential pressure transducer (model DP45-14, Validyne, Northridge, CA). $\dot{V}O_2$ and $CO_2$ production were determined from these measurements. The coefficient of variation in $\dot{V}O_2$ and $CO_2$ production over several days in a single subject is 5% in our laboratory.

On each of the six experimental days, 3 ml of arterial blood were sampled at each exercise level and subsequently analyzed for lysed whole blood lactate (2300 Stat Plus, YSI, 482 AUTONOMIC NERVOUS SYSTEM AND CARDIAC OUTPUT AT ALTITUDE

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Age, yr</th>
<th>Weight, kg</th>
<th>Height, m</th>
<th>Sea-Level $V_{O_2\max}$, ml min⁻¹ kg⁻¹</th>
<th>Maximal Work, W</th>
<th>Vital Capacity, %pred</th>
<th>FEV1, %pred</th>
<th>FEV1/Vital Capacity, %pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>32 ± 4</td>
<td>69.5 ± 6.5</td>
<td>1.72 ± 0.03</td>
<td>43 ± 11 k</td>
<td>280 ± 72*</td>
<td>103 ± 7</td>
<td>99 ± 6</td>
<td>103 ± 4</td>
</tr>
<tr>
<td>35 ± 7†</td>
<td>230 ± 48†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD. $V_{O_2\ max}$, maximal $O_2$ consumption; FEV1, forced expiratory volume in 1 s; %pred, expressed as percentage of that predicted. *Exercise in normoxia; †exercise in hypoxia.
Table 2. Peak exercise data at SL and at WM under different drug regimens and with varying $F_{O_2}$

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Control</th>
<th>Propranolol</th>
<th>Glycopyrrolate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SL</td>
<td>WM</td>
<td>SL</td>
<td>WM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal work, W</td>
<td>263 ± 21</td>
<td>275 ± 23</td>
<td>263 ± 19</td>
<td>263 ± 21</td>
</tr>
<tr>
<td></td>
<td>216 ± 14</td>
<td>224 ± 12</td>
<td>216 ± 14*</td>
<td>212 ± 15*</td>
</tr>
<tr>
<td></td>
<td>3.01 ± 0.21</td>
<td>2.82 ± 0.20</td>
<td>2.97 ± 0.19*</td>
<td>2.85 ± 0.28*</td>
</tr>
<tr>
<td></td>
<td>2.39 ± 0.19*</td>
<td>2.37 ± 0.16*</td>
<td>2.51 ± 0.17*</td>
<td>2.24 ± 0.19*</td>
</tr>
<tr>
<td>$S_{aO_2}$, %</td>
<td>98 ± 1</td>
<td>99 ± 0</td>
<td>99 ± 0</td>
<td>99 ± 0</td>
</tr>
<tr>
<td></td>
<td>81 ± 1*</td>
<td>84 ± 2†</td>
<td>79 ± 1*</td>
<td>87 ± 2‡</td>
</tr>
</tbody>
</table>

Values are means ± SD. SL, sea level; WM, 2-wk at 3,800 m; $F_{O_2}$, inspiratory fraction of $O_2$; $V_{O_2}$, $O_2$ uptake; $S_{aO_2}$, arterial $O_2$ saturation. Normoxia = ambient air at SL and $F_{O_2}$ of 0.34 at WM. Hypoxia = $F_{O_2}$ of 0.125 at SL and ambient air at WM. *$P < 0.01$ for normoxia vs. hypoxia; †$P = 0.05$ for SL vs. WM; ‡$P = 0.002$ for SL vs. WM.
chronic hypoxia not significant) and was similar to SL values with low \( P_{\text{O}_2} \) (Fig. 1). The reduction in WM peak HR induced by propranolol was compensated for by an increase in WM peak stroke volume (propranolol vs. control: \( P < 0.002 \) in hypoxia and \( P < 0.005 \) in normoxia). Despite a numerically lower stroke volume after glycopyrrolate (higher HR without change in \( Q_{\dot{\text{T}}} \)), the reduction in stroke volume did not reach statistical significance (\( P = 0.036 \), not significant with Bonferroni correction) because of the combined random errors in the independently measured HR and \( Q_{\dot{\text{T}}} \).

**DISCUSSION**

The main findings of the present study are that, at WM, 1) \( Q_{\dot{\text{T}}} \) at peak exercise for subjects breathing air at this altitude was 18% lower than at SL before ascent; 2) maximal \( Q_{\dot{\text{T}}} \) was immediately restored to levels not significantly different from SL values when exercise was performed in normoxia; 3) propranolol reduced and glycopyrrolate increased maximal HR, without significant effects on maximal \( Q_{\dot{\text{T}}} \). Also, although \( V_{\text{O}_2} \) max and power outputs were both reduced by hypoxia, neither propranolol nor glycopyrrolate reduced these variables at SL or WM.

Thus we confirmed the basic observations made previously in others in points 1 and 2 above (1, 32, 43, 46). In addition, the effects of sympathetic and parasympathetic blockade on HR and exercise capacity were similar as in previous studies (14, 29). Overall, these results confirm the adequacy of our dosing of propranolol and glycopyrrolate and therefore establish the setting required to test the hypothesis of this paper: that the ANS reduction of HR is not responsible for the reduced maximal \( Q_{\dot{\text{T}}} \) at altitude. It is, however, appropriate to point out that, based on just five subjects, the conclusions of this study need to be made with some caution despite their statistical significance.
Attainment of peak \( \dot{V}O_2 \) under all conditions. Before dealing with any explanation for the reduced maximal \( \dot{Q}_T \) at altitude, the issue of whether our subjects reached peak \( \dot{V}O_2 \) must be discussed. There were no significant differences in peak \( \dot{V}O_2 \) or workload in any of the different exercise bouts (at SL or WM), including those of the preliminary test, under similar \( P_{O_2} \). Evidence for maximum effort in the preliminary test comes from the fact that peak HR was higher than 95% of the age predicted maximum in all subjects. Additionally, the peak exercise respiratory exchange ratios were 1.09 ± 0.01 and 1.11 ± 0.01 in normoxia and hypoxia, respectively. Lysed whole blood lactate concentrations of 9.7 ± 0.8 and 8.2 ± 0.7 mmol/l and norepinephrine concentrations of 2,813 ± 359 and 2,727 ± 384 pg/ml were observed, respectively. Together, these findings support the conclusion that subjects attained peak \( \dot{V}O_2 \) under all experimental conditions.

\( \text{C}_2\text{H}_2 \) uptake method for measuring \( \dot{Q}_T \). Because of the large number of individual measurements of peak \( \dot{Q}_T \) performed in each subject (about 60 determinations in each subject, spread over 12 exercise sessions on 6 different days), it was critical that a noninvasive method was used. Because of the motion associated with exercise, the only class of noninvasive techniques that could be used had to be based on gas exchange. A further critical constraint was that, at all exercise levels in both normoxia and hypoxia, alveolar \( P_{O_2} \) and \( P_{CO_2} \) during the periods of \( Q_T \) measurement had to be maintained at the levels occurring naturally at the designated \( P_{O_2} \) during each exercise bout before and after such measurements. This was important because acute changes in \( P_{O_2} \) can change \( \dot{Q}_T \) and HR within seconds, thus invalidating the entire study. The short-term \( \text{C}_2\text{H}_2 \) uptake method (3) was developed for just this circumstance. It requires only that the subject be switched from the particular inspired \( O_2-N_2 \) gas mix dictated by the protocol to a gas mix of the same \( P_{O_2} \) containing trace levels of \( \text{C}_2\text{H}_2 \) and He for ~20 breaths. Moreover, during these 20 breaths, the subject continues to breathe exactly as during the remainder of the exercise segment. Rebreathing methods on the other hand (\( \text{CO}_2 \) or \( \text{C}_2\text{H}_2 \)) have the potential of causing substantial changes in alveolar \( P_{O_2} \) and/or \( P_{CO_2} \), unless special precautions are taken to buffer inhaled levels of these gases, a difficult task. Thus the \( \text{C}_2\text{H}_2 \) uptake method was selected as the most appropriate technique for our particular protocol design. This required measurements of \( \text{C}_2\text{H}_2 \) partition coefficient in each subject on every study day, both at rest and during exercise, to be sure that apparent differences in \( \dot{Q}_T \) were not the result of changes in \( \text{C}_2\text{H}_2 \) solubility under any condition. Our data therefore reflect the use of each subject’s own solubility data for each exercise session. In the paper by Barker et al. (3), the \( \text{C}_2\text{H}_2 \) method was validated against the direct Fick method and found to agree well. Johnson et al. (20) compared \( \text{C}_2\text{H}_2 \) uptake data (by using two computational methods different from ours) with the Fick method and found strong correlations (\( r^2 = 0.89 \) to 0.90). However, \( \dot{Q}_T \) was underestimated significantly with the use of one of these two calculation techniques, likely a result of either increased ventilation-perfusion (\( V_{A}/Q \)) inequality or failure to account for \( \text{C}_2\text{H}_2 \) recirculation to the lungs at high levels of exercise. Therefore, an important constraint on the use of such methods is their vulnerability to underestimation of \( \dot{Q}_T \) in the presence of \( V_{A}/Q \) inequality. Our laboratory noted previously that exercise, especially in hypoxia, causes an increase in \( V_{A}/Q \) inequality (12). Thus the hypoxic \( \dot{Q}_T \) values during peak exercise could be somewhat lower than the actual values. This is unlikely to affect interpretation of the present study for two reasons. First, the important comparison was for maximal \( \dot{Q}_T \) for subjects breathing ambient air at 3,800 m between control conditions, after propranolol, and after glycopyrrolate. The peak work rates and \( \dot{V}O_2 \) were unaffected by the two drugs (see RESULTS), and the study design used each subject as their own control. Thus, even if \( V_{A}/Q \) inequality led to an underestimate of \( \dot{Q}_T \), the relative values under the three conditions should be comparable. The second reason comes from a study of the quantitative effects of \( V_{A}/Q \) inequality on \( \text{C}_2\text{H}_2 \)-based \( \dot{Q}_T \) measurements, for which we constructed a two-compartment tidally ventilated model of \( V_{A}/Q \) mismatch and computed the effects of increasing degrees of \( V_{A}/Q \) inequality on the estimated \( \dot{Q}_T \). The increase in \( V_{A}/Q \) inequality from rest to exercise, even in hypoxia, is relatively small: log \( SD_Q \), the second moment of the perfusion distribution, increasing from ~0.4 to ~0.6 (12). This change was calculated to spuriously decrease estimated \( \dot{Q}_T \) by only 3%, a perturbation that would be very difficult to detect experimentally.

Possible mechanisms of reduced maximal \( \dot{Q}_T \) after altitude acclimatization. Several cardiocirculatory adaptations have been proposed to explain the reduced maximal \( \dot{Q}_T \). It is known that hypoxia acutely increases Hb concentration, implying water shifting out of the plasma space (31). Subsequent altitude acclimatization results in further plasma volume reduction through greater sweating, respiration, and urine production. This plasma volume loss is enhanced by a reduction in plasma oncotic pressure due to net protein loss. In our study, Hct was elevated by 16% from 43 to 50%. Because it takes more than 2 wk before hypoxia-induced increases in erythropoiesis can significantly increase erythrocyte volume (11), plasma volume in our subjects must have been lower at WM than at SL (but we did not measure plasma volume). Accordingly, reduced cardiac filling pressures might have limited maximal \( \dot{Q}_T \) in our subjects. Although acclimatization-related changes in cardiac filling pressures were clearly shown by Reeves et al. (33) and Boussuges et al. (5), there is evidence against the hypothesis that they lead to a reduced maximal \( \dot{Q}_T \). In those studies where blood volume was expanded, there was little or no augmentation in maximal \( \dot{Q}_T \) (10, 14, 47). Moreover, acute \( O_2 \) breathing at altitude causes maximal exercise capacity and \( \dot{Q}_T \) to rise (32) without changing blood volume. Such was the case in the present study, where breathing 34% \( O_2 \) at altitude elevated \( \dot{Q}_T \) and \( \dot{V}O_2 \) to
values that were not significantly different from SL normoxic values. However, the possibility of a type II error cannot be ruled out. Nevertheless, Robach et al. (37) recently reported a 9% increase in $V_{O_2}$max with plasma volume expansion in subjects exercising at a simulated altitude of 6,000 m.

The elevation in Hb with acclimatization increases blood viscosity, which might affect maximal $Q_T$ (36). Opposing this theory is the fact that isovolemic hemodilution does not restore maximal $Q_T$ or exercising muscle blood flow (18). Even stronger evidence against this hypothesis comes, again, from the increased maximal exercise capacity and $Q_T$ on breathing supplemental oxygen. This increase is established without changing Hct.

At altitude, the myocardium may self-limit its own pumping function because of limited myocardial $O_2$ availability (1, 30). This seems unlikely because even those subjects acclimatized to the extreme altitude of the summit of Mt. Everest (8,848 m, barometric pressure = 253 Torr, arterial $P_{O_2} = \sim 25–30$ Torr) showed no evidence of impaired cardiac function by symptoms, echocardiography, or ECG. In Operation Everest III, a modification was found of left ventricular filling pattern but no change of myocardial contractility or $Q_T$ (5). Our subjects conformed to these findings in that ECG remained normal and there were no ischemic symptoms. This leaves ANS changes and reduced work rate as the most probable remaining possibilities.

ANS changes with altitude. It has been shown that with time at altitude, adaptations occur in the ANS and that they result in an altered HR response to exercise. These adaptations consist of increased sympathetic activation as evidenced by higher circulating norepinephrine and muscle sympathetic nerve activity (25, 27, 39). However, there is also evidence of cardiac β-receptor desensitization (2, 21, 34, 35) and increased cholinergic activation (22). Prolonged exposure to altitude and, hence, prolonged exposure to high levels of adrenergic agonists can be expected to result in a decline in mRNA encoding the $\beta_2$-adrenergic receptor. This process of long-term desensitization should be considered separately from short-term desensitization and leads to lower quantities of receptors at the membrane level (13). The effects of acclimatization and autonomic blockade on the HR response to exercise that we found (lower maximal HR under control conditions, further reduction with sympathetic blockade, increase to SL maximum with parasympathetic blockade) are similar to those found in previous studies (15, 40). However, up until now, it has not been determined whether the reduced maximal HR is responsible for reduced maximal $Q_T$ or, rather, is compensated for by an increase in stroke volume. In previous studies, the effects of autonomic blockade on exercise $Q_T$ have been investigated at SL (ambient air) only, showing a slight reduction in maximal $Q_T$ with propranolol and no effect of parasympathetic blockade with atropine or glycopyrrolate (7). The present study confirms these results and, moreover, shows that these drug effects are similar after altitude acclimatization.

The large increases in norepinephrine concentrations (at rest from 388 ± 49 pg/ml at SL to 759 ± 67 pg/ml at WM, and at peak exercise from 2,813 ± 359 pg/ml at SL to 3,506 ± 668 pg/ml at WM, both $P < 0.001$) confirm that, in our subjects, acclimatization resulted in an increase of sympathetic activation. Two findings in the present study argue against an important role of

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**Fig. 3.** Correlations between peak exercise cardiac index ($Q_T$ indexed for body surface area, expressed in ml·min⁻¹·m⁻²) and peak arterial $O_2$ saturation ($SaO_2$; in %; A), peak oxygen delivery index (oxygen delivery indexed for body surface area, expressed in arbitrary units; B), peak oxygen extraction (in %; C), and peak $O_2$ consumption ($V_{O_2}$; in ml·min⁻¹·m⁻²; D) in 5 subjects exercising in hypoxia: $P_{O_2} = 0.125$ at SL and ambient air after 2 wk of acclimatization at 3,800 m. altitude (WM). Exercise was performed either without drug, under sympathetic blockade with propranolol, or under parasympathetic blockade with glycopyrrolate. When between-subject variability is taken into account for this repeated-measures regression, only A ($P = 0.0004$) and D ($P = 0.03$) are significant. See text for details.
this activation in the reduced maximal \( Q_T \) with altitude. First, the reduction in maximal \( Q_T \) with acclimatization was not significantly affected by either propranolol or glycopyrrolate in doses sufficient to greatly alter HR. Second, acute \( O_2 \) breathing at WM resulted in an immediately higher \( Q_T \), without sufficient time for an increase in \( \beta \)-receptor mRNA levels to compensate for long-term desensitization, as described above.

The passive hypothesis. With little or no evidence to support the aforementioned explanations for reduced maximal \( Q_T \) (reduced blood volume, increased viscosity, myocardial hypoxia, or autonomic changes), we are left with the passive hypothesis as the best explanation for the findings. This hypothesis states that at any level of exercise, \( Q_T \) is dictated by \( V_O_2 \). Certainly, there is a tight linear relationship between \( Q_T \) and \( V_O_2 \) from rest to \( V_O_2_{max} \). The slope and intercept of this relationship are very similar across many published studies in normoxia (16, 19, 23, 28, 41). Whereas the intercept is higher in acute hypoxia, the slope is not (46), and, after acclimatization, the relationship returns to that of normoxia (4, 32, 33). Our understanding of the underlying mechanisms that may tie \( Q_T \) to \( V_O_2 \) is vague, but it is possible that predominantly local muscle metabolic and neural changes with exercise could dictate local vascular conductance. This in turn could signal an increase in \( Q_T \) to maintain systemic pressure via further neural and humoral pathways (38). In this scenario, the lower maximal \( Q_T \) would be the regulated result of the lower maximal power output and \( V_O_2 \) at altitude.

Consequences of changes in maximal \( Q_T \) for \( O_2 \) transport in hypoxia. Theoretical and experimental work suggests that, at altitude, gains in convective \( O_2 \) transport in the circulation that might be afforded by an increase in \( Q_T \) would be partially offset by corresponding reductions in the diffusive transport of \( O_2 \) from alveolar gas to pulmonary capillary blood and from microvascular blood to muscle mitochondria (44, 45). Somewhat by chance, the present study provides experimental data to partially test this hypothesis. Figure 3A shows the relationship between cardiac index (\( Q_T \) divided by body surface area) and \( S_AO_2 \) at maximal exercise across the six conditions involving hypoxia (three at SL and three at WM, each under control conditions, postpropranolol, and postglycopyrrolate). Each of the five subjects is shown separately (each represented by a different symbol). There is a clear inverse relationship between the two variables compatible with the idea that, due to diffusion limitation in the lungs during hypoxic exercise, increases in \( Q_T \) further impair \( O_2 \) loading in the lungs because of decreased pulmonary capillary transit times. The inverse relationship between cardiac index and \( S_AO_2 \) not only holds for all data grouped together but, more importantly, within the data sets of each single subject. The mean slope of this relationship is \(-3.7\) and is significantly different from 0 (\( P < 0.0001; \ P = 0.0004 \) for regression lines in individual subjects). This slope translates to a mean fall of 1.5% in \( S_AO_2 \) per liter per minute increase in \( Q_T \). Whether this is cause and effect, Figure 3B shows that, within each individual subject, systemic oxygen delivery (indexed to body surface area) does not change with increasing cardiac index across the same six hypoxic conditions (the individual slopes are not different from 0). Thus the gain in delivery that would result from increased \( Q_T \) is offset by a lower \( S_AO_2 \). The correlation between cardiac index and oxygen delivery for the grouped data is misleading. This positive correlation is due to between-subject differences in exercise capacity (the likely result of differences in fitness, genetics, and so forth) with subsequent differences in both cardiac index and oxygen delivery, and the relationship accounting for repeated delivery and the relationship accounting for repeated differences in exercise capacity (the likely result of differences in fitness, genetics, and so forth) with subsequent differences in both cardiac index and oxygen delivery, and the relationship accounting for repeated measures on individuals is not significant (\( P = 0.52 \)). Accordingly, \( O_2 \) extraction (Fig. 3C, calculated by dividing \( V_O_2 \) by oxygen delivery) does not change over the cardiac index range: the slope of the overall regression line is not significantly different from 0 (\( P = 0.12 \)). This plot shows a lot of scatter, probably due to the fact that the variable is not directly measured. Instead, it was derived indirectly from \( Q_T \), \( Hct \), \( S_AO_2 \), and \( V_O_2 \), thereby amplifying the separate measurement errors. Finally, Fig. 3D shows the relationship between peak cardiac index and peak \( V_O_2 \). Again, the individual regression lines give a picture different from the overall regression line. Overall, there is a highly significant positive correlation with a slope of 0.164, which is to be expected for exercise at moderate altitude. Knowing the average \( S_AO_2 \) under these circumstances (~80%), it can be calculated that, with every liter per minute per meter squared increase in cardiac index, oxygen delivery per meter squared is 160 ml higher, and, therefore, \( V_O_2 \) can theoretically increase by ~160 ml min\(^{-1} \) m\(^{-2} \).

The individual lines, however, have much lower slopes. The average slope is 0.05, which is significantly different from both 0 (\( P = 0.03 \)) and 0.164 (\( P = 0.002 \)). This means that, within individuals, the sensitivity of peak \( V_O_2 \) to an increase in \( Q_T \) is lower, at about one-third of the value expected if \( Q_T \) were the dominant limiting factor. This is concordant with the concept that, at or near maximal exercise at moderate altitude, the benefits of an increase in convective \( O_2 \) transport will largely be offset by a decrease in diffusive \( O_2 \) transport (44).

Conclusions. Of the several theories advanced to explain why maximal exercise \( Q_T \) is reduced after acclimatization at altitude, that implicating the ANS as the major factor is not supported by the results of the present study. This is despite the documented changes in the ANS, including cardiac \( \beta \)-receptor desensitization shown by the previous work of other authors (21, 33, 34). Thus separate sympathetic and parasympathetic blockade, although producing the expected changes in HR, had no significant effects on maximal exercise capacity or \( Q_T \) at altitude. Combined with the immediate normalization of maximal \( Q_T \) at altitude when high \( O_2 \) concentrations are breathed seen in the present and many prior studies, the likeliest cause of diminished peak \( Q_T \) is increased demand caused by hypoxic limitation of muscle metabolic rate.
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