

Parasympathetic Neural Activity Accounts for the Lowering of Exercise Heart Rate at High Altitude

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Background—In chronic hypoxia, both heart rate (HR) and cardiac output (Q) are reduced during exercise. The role of parasympathetic neural activity in lowering HR is unresolved, and its influence on Q and oxygen transport at high altitude has never been studied.

Methods and Results—HR, Q, oxygen uptake, mean arterial pressure, and leg blood flow were determined at rest and during cycle exercise with and without vagal blockade with glycopyrrolate in 7 healthy lowlanders after 9 weeks' residence at ≥ 5260 m (ALT). At ALT, glycopyrrolate increased resting HR by 80 bpm (73 ± 4 to 153 ± 4 bpm) compared with 53 bpm (61 ± 3 to 114 ± 6 bpm) at sea level (SL). During exercise at ALT, glycopyrrolate increased HR by ≈ 40 bpm both at submaximal (127 ± 4 to 170 ± 3 bpm; 118 W) and maximal (141 ± 6 to 180 ± 2 bpm) exercise, whereas at SL, the increase was only by 16 bpm (137 ± 6 to 153 ± 4 bpm) at 118 W, with no effect at maximal exercise (181 ± 2 bpm). Despite restoration of maximal HR to SL values, glycopyrrolate had no influence on Q, which was reduced at ALT. Breathing $F_{iO_2} = 0.55$ at peak exercise restored Q and power output to SL values.

Conclusions—Enhanced parasympathetic neural activity accounts for the lowering of HR during exercise at ALT without influencing Q. The abrupt restoration of peak exercise Q in chronic hypoxia to maximal SL values when arterial PO_2 and SO_2 are similarly increased suggests hypoxia-mediated attenuation of Q. (*Circulation*. 2001;104:1785-1791.)

Key Words: heart rate ■ cardiac output ■ hypoxia ■ nervous system, autonomic ■ exercise

Acclimatization to high altitude induces alterations in autonomic neural control of the cardiovascular system, exemplified by a marked reduction in maximal heart rate (HR).¹⁻⁴ Christensen and Forbes¹ first described the reduction in peak exercise HR at high altitude in 1937, yet the mechanism underlying this response has remained elusive for >60 years. Adaptations in both parasympathetic and sympathetic neural tone have been implicated in the relative bradycardia response to exercise in chronic hypoxia. A progressive influence of parasympathetic activity on HR occurs with duration of altitude exposure either via a central effect of hypoxia,^{4,5} by greater influence at the cardiac receptor level,⁶⁻⁸ or by cholinergic antagonism.⁹ It has not been clearly shown whether enhanced vagal tone actually causes the lower HR, ie, by a direct adaptation to hypoxia, or whether a greater vagal influence is exhibited due to a lowering of HR by another mechanism, eg, lower sympathetic activation, reduced cardiac sensitivity to adrenergic stimulation, or modulation by other (eg, adenosinergic) receptors.^{8,10,11} Furthermore, studies on parasympathetic neural control of HR in hypoxia have yielded discrepant findings.^{4,12,13} The functional significance of vagal control of HR at altitude for systemic oxygen transport and hemodynamic

responses has also never been studied. In this regard, a reduction in maximal cardiac output (Q) and oxygen delivery during exercise has also been documented with altitude acclimatization,^{3,14-17} yet it is unknown whether this is a result of parasympathetic neural control of HR. Accordingly, the purpose of this study was to ascertain the influence of the parasympathetic nervous system on HR, Q, systemic hemodynamics, and oxygen uptake ($\dot{V}O_2$) at rest and during dynamic exercise after prolonged exposure to high altitude (9 weeks' residence at ≥ 5260 m).

Methods

Seven healthy Danish lowlanders (4 men; 3 women) 23 ± 2 years old gave informed consent to participate in the study, which was approved by the ethical committee of Copenhagen and Frederiksberg. All subjects performed submaximal and maximal cycle ergometer exercise under control conditions and parasympathetic blockade with glycopyrrolate (0.8 mg) at sea level and at altitude after 9 weeks' residence at ≥ 5260 m above sea level, during which time HR, Q, mean arterial pressure (MAP), leg blood flow (LBF), and $\dot{V}O_2$ were measured.

Under local anesthesia, catheters were placed in the femoral artery and vein by use of the Seldinger technique. Q was measured by indocyanine green (ICG, Akorn Inc) dye dilution.¹⁸ Five to 8 mg of dye was injected rapidly into the femoral vein, followed by a 10-mL

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flush of isotonic saline. Blood from the femoral artery was withdrawn by a pump at 20 mL/min through a linear photodensitometer (Waters Instruments Inc) for measurement of the arterial dye concentration. The dye curves were displayed on a chart recorder (Gould 8000) and extrapolated with a logarithmic scale based on the exponential decay (downslope) observed from 75% to 50% of the peak dye concentration to correct for recirculation. Q was then computed as the ratio of dye injected to the average arterial ICG concentration over the time interval of the curve and expressed per minute. After each experiment, an ICG calibration curve was derived from measurement of the deflection from 3 separate 25-mL blood samples with various concentrations of ICG.

LBF was measured in the femoral vein by constant-infusion thermodilution as described by Andersen and Saltin.¹⁹ Constant infusion of ice-cold saline was performed at variable rates to reduce blood temperature at the thermistor by $\approx 1^\circ\text{C}$. Both blood and infusate temperatures were monitored continuously during infusion by thermistors connected to the venous catheter and to the data acquisition system. Blood flow was calculated on the basis of the thermal balance principle as described previously.¹⁹

Blood was sampled anaerobically from the artery and vein simultaneously for measurement of O_2 saturation and content (Oxy-lite, Radiometer). Plasma norepinephrine and epinephrine concentrations were measured by high-performance liquid chromatography with electrochemical detection.²⁰ Leg $\dot{V}\text{O}_2$ was determined by the product of the arteriovenous O_2 difference and blood flow. MAP was taken as the average of systolic and diastolic pressures determined by a transducer (Baxter) positioned at heart level, connected to the arterial catheter, and interfaced to an online monitor (Dialogue 2000, Danica) and data acquisition system (MacLab AD Instruments). HR was determined from an ECG interfaced with the data acquisition system. As a rough estimate of myocardial oxygen demand, the rate-pressure product was calculated as the product of HR and MAP. Total peripheral resistance (TPR) was derived from the ratio of MAP to Q, and leg vascular resistance was taken as the ratio of MAP to LBF. Pulmonary $\dot{V}\text{O}_2$ was measured with a metabolic cart (Medical Graphics CPX).

Measurements were obtained at rest, after 5 minutes of steady-state submaximal cycling at ≈ 118 W, and again at maximal exertion (227 W at altitude; 280 W at sea level). The control experiment was performed first, followed by the parasympathetic blockade trial. To examine the influence of inspired O_2 concentration (FIO_2) on the control of HR and Q during exercise at altitude, subjects also breathed an air mixture containing 55% O_2 from Douglas bags at the end of the maximal exercise load during the control trial at 5260 m. This inspired O_2 fraction equaled the ambient PO_2 at sea level. Q was measured within 1 minute after the O_2 -enriched air mixture was introduced. The subjects then continued to cycle at higher loads until exhaustion was reached, and Q was measured again just before the end of voluntary work.

At the end of the control experiment, the subjects rested supine for 2 hours before repeating the trial with glycopyrrolate. To assess the efficacy of parasympathetic blockade, the HR response to incremented doses of glycopyrrolate was monitored at rest at sea level. Subjects were monitored for 5 minutes after repeated intravenous injection of 0.2 mg glycopyrrolate and continuing until a plateau HR was achieved.

Data Analysis

All data are expressed as mean \pm SEM. Comparisons between conditions and exercise loads were analyzed with Friedman's test, and specific differences between the means were located with Wilcoxon's test. Probability was considered to be significant at a value of $P < 0.05$.

Results

The grouped mean resting HR responses to incremental doses of glycopyrrolate at sea level are shown in Figure 1. Significant increases in HR from the control resting level of 61 ± 3 bpm occurred at glycopyrrolate doses > 0.4 mg, and a ceiling

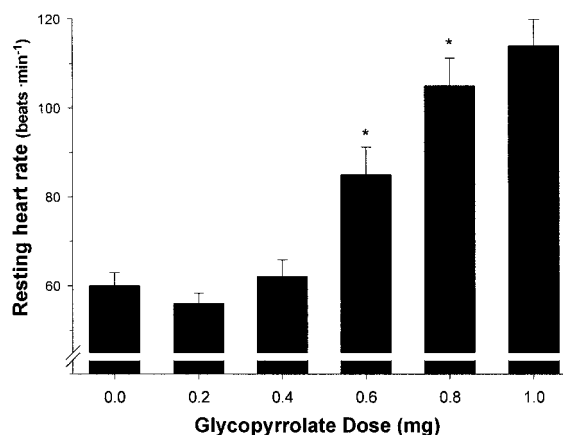


Figure 1. Resting HR responses at sea level during progressive intravenous doses of glycopyrrolate. Glycopyrrolate (0.2 mg) was introduced every 5 minutes up to a peak dose of 1.0 mg. Values are mean and SEM. *Increase above previous dose ($P < 0.05$).

of HR at 114 ± 6 bpm was reached after 0.8 mg, indicating complete parasympathetic blockade ($P < 0.05$). A higher dose of 1.0 mg elicited no further increase in HR. The increment in resting HR after complete parasympathetic blockade at sea level was 53 bpm (61 ± 3 to 114 ± 6 bpm) (Figure 2). In contrast, after 9 weeks of acclimatization to ≥ 5260 m, parasympathetic blockade increased resting HR 80 bpm (from 73 ± 4 to 153 ± 4 bpm) ($P < 0.05$).

During submaximal cycle exercise (118 W) at sea level, glycopyrrolate increased HR 16 bpm (137 ± 6 to 153 ± 4 bpm) ($P < 0.05$), but at the maximal workload, HR was unaffected by glycopyrrolate (Figure 2). In contrast, after 9 weeks' residence at ≥ 5260 m, glycopyrrolate increased HR 43 bpm during submaximal exercise (127 ± 4 to 170 ± 3 bpm; 118 W) and 39 bpm (141 ± 6 to 180 ± 2 bpm) at maximal exercise ($P < 0.05$). After long-term altitude exposure, the increase in HR at rest with glycopyrrolate was 13 bpm higher than the peak HR observed during maximal control exercise at altitude.

Compared with sea level, peak power output was reduced by 20% at altitude, along with a similar decrement in Q (Figure 2) and LBF and a 40% reduction in pulmonary $\dot{V}\text{O}_2$ (Figure 3). Also, compared with sea level, MAP was significantly higher during exercise at altitude (Figure 3), accompanied by elevated plasma norepinephrine and epinephrine (Figure 4).

Both at sea level and after long-term altitude exposure, parasympathetic blockade exerted no influence on Q, MAP, $\dot{V}\text{O}_2$, or vascular resistances at rest or during exercise. Stroke volume was reciprocally reduced with parasympathetic blockade (Figure 2) as HR was elevated, leaving Q unchanged compared with control conditions. The rate-pressure product, reflecting only a rough estimate of myocardial oxygen demand, was similar between sea-level and long-term altitude control conditions. With parasympathetic blockade at altitude, however, the rate-pressure product was higher than under control altitude and sea-level conditions, as shown in Figure 5. Under control conditions at altitude, the rate-

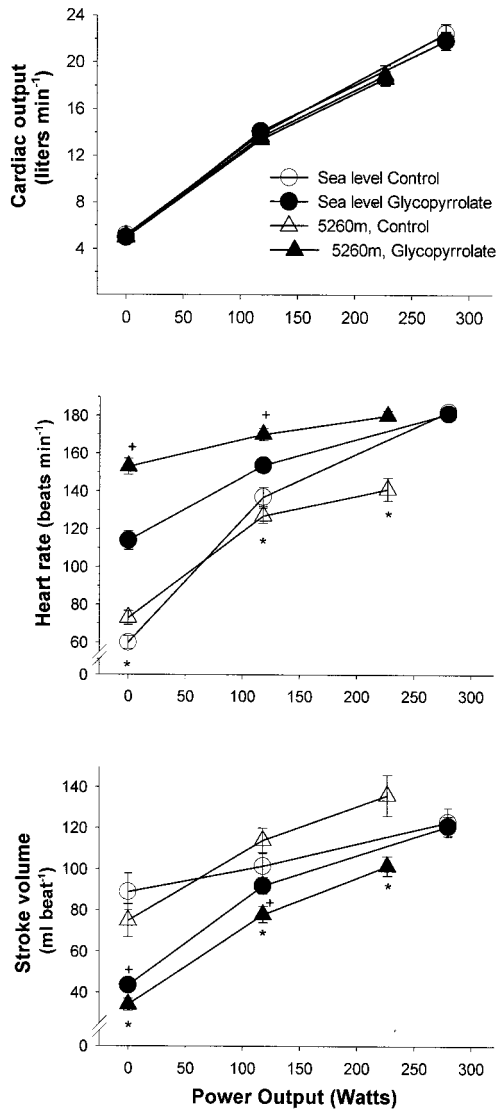


Figure 2. Q (top), HR (middle), and stroke volume (bottom) at rest and during submaximal and maximal cycling exercise. Values are mean and SEM. Despite marked variations in HR and stroke volume induced by altitude (5260 m) and/or glycopyrrolate, Q remains unchanged for a given power output. Same peak HR was observed at altitude and sea level with glycopyrrolate. *Difference between control sea level and control 5260 m; + difference between glycopyrrolate sea level and glycopyrrolate 5260 m ($P < 0.05$).

pressure product was similar to that under control sea-level conditions.

The influence of 0.55 F_{IO_2} on HR and Q during exercise at 5260 m is shown in Figure 6. After the subjects had reached their peak exercise load breathing ambient air, switching to 0.55 F_{IO_2} resulted in a rapid increase in Q (from 19 ± 0.8 to 21.7 ± 1 L/min) and HR (from 141 ± 6 to 156 ± 6 bpm) at the same work rate ($P < 0.05$). They were then able to continue to a higher Q (23 ± 1 L/min), HR (176 ± 3 bpm), and power output (280 W), which were all similar to the sea-level values ($P < 0.05$). These responses were associated with dramatic increases in P_{aO_2} (from 46 ± 1 to 135 ± 7 mm Hg), S_{aO_2} (from $73 \pm 2\%$ to $97 \pm 6\%$), and Ca_{O_2} (from 19.6 ± 1 to 26 ± 0.8 mL/100 mL) (Figure 7) ($P < 0.05$) and decreases in MAP

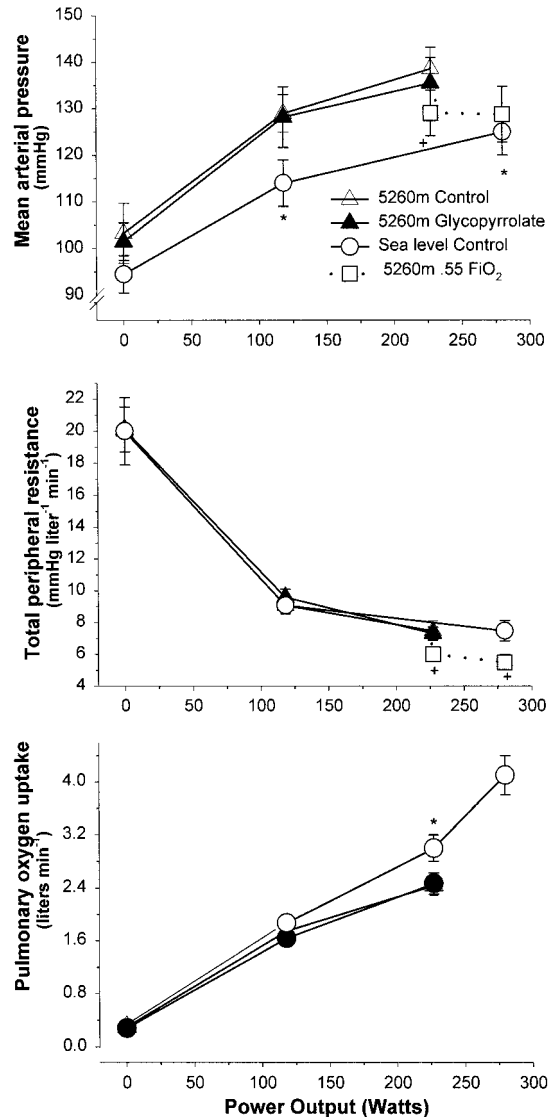


Figure 3. MAP (top), TPR (middle), and pulmonary $\dot{V}O_2$ (bottom) at rest and during submaximal and maximal cycling exercise at sea level and after 9 weeks' residence at high altitude (5260 m). Values are mean and SEM. □, Responses at peak exercise after oxygen supplementation ($F_{IO_2} 0.55$). No differences ($P > 0.05$) were seen in these hemodynamic responses between control and glycopyrrolate trials. *Difference between sea level and 5260 m ($P < 0.05$); + significant effect of oxygen supplementation.

(from 138 ± 4 to 129 ± 5 mm Hg) and TPR (from 7.5 ± 0.6 to 6 ± 0.3 mm Hg \cdot L⁻¹ \cdot min⁻¹) ($P < 0.05$) in response to breathing 0.55 F_{IO_2} (Figure 3).

Discussion

There were 2 major findings in this study. First, the pronounced elevation of HR observed both at rest and during exercise with vagal blockade after 9 weeks' residence at 5260 m implicates enhanced parasympathetic activity as the primary mechanism underlying the well-known reduction in exercise HR at altitude. Although other adaptations may have coexisted, this study shows that the reduction in exercise HR is completely accounted for by increased parasympathetic

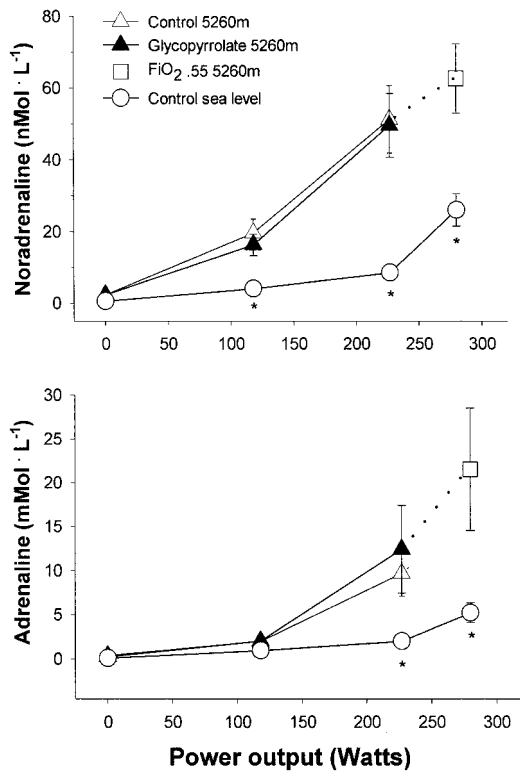


Figure 4. Arterial plasma norepinephrine (top) and epinephrine at sea level and after 9 weeks' residence at 5260 m. Values are mean and SEM. *Difference from responses at 5260 m ($P < 0.05$).

neural activity. The 80-bpm increase in HR at rest and ≈ 40 bpm elevation during both submaximal and maximal exercise at 5260 m with glycopyrrolate represent the largest range of parasympathetic control of HR ever reported either at altitude or at sea level. In comparison, Hartley et al⁴ found that atropine increased maximal HR 10 bpm after 1 week at 4600 m, and Savard⁶ reported a 20-bpm increment in maximal HR after 6 weeks at 5000 to 6000 m. In contrast to the pronounced influence on HR at altitude in this study, parasympathetic blockade at sea level resulted in only a 16-bpm increase in HR during submaximal exercise and had no effect at maximal exercise, responses of which are in agreement with previous reports.^{21,22} The finding that resting HR with parasympathetic blockade at altitude (153 ± 4 bpm) was higher than control HR at maximal exercise (141 ± 6 bpm) clearly demonstrates the important role of the parasympathetic nervous system for attenuating maximal HR in chronic hypoxia. Furthermore, with vagal blockade at high altitude, maximal exercise HR was the same as that at sea level. The findings in this study, along with those of Hartley et al⁴ and Savard et al,⁶ demonstrate that in contrast to sea level, vagal control in chronic hypoxia is exerted over the entire range of HRs from rest to maximum.

Despite enhanced vagal activity, the ≈ 15 -bpm-higher resting HR at altitude compared with sea level, together with the dramatic increase in HR at rest with parasympathetic blockade, indicate that after prolonged acclimatization, there is enhanced basal sympathetic activity. Parallel studies at altitude involving direct neurographic recordings of muscle

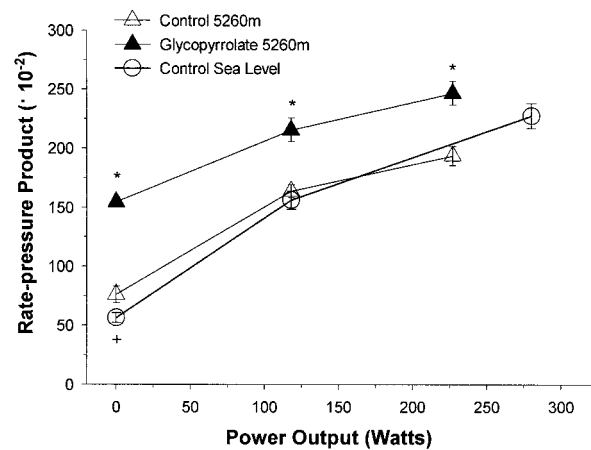


Figure 5. Rate-pressure product of HR and MAP as index of myocardial work at rest and during exercise in control and glycopyrrolate trials after 9 weeks' residence at high altitude (5260 m) and in sea-level control conditions. Values are mean and SEM. *Difference between control 5260 m and glycopyrrolate 5260 m; +difference between all conditions ($P < 0.05$).

sympathetic nerve activity revealed a 400% increase in resting sympathetic discharge compared with sea level,²³ which is consistent with the dramatically elevated plasma norepinephrine levels (Figure 4). It has been hypothesized that the reduction in maximal HR at altitude may be accounted for in part by reduced cardiac β -receptor density or sensitivity.^{8,10,11} Yet, the parity of maximal exercise HR during vagal blockade at altitude (180 ± 3 bpm) with the control maximal values observed at sea level (181 ± 2 bpm) indicates that sympathetic adrenergic control of HR is not attenuated after prolonged acclimatization. The possibility of β -receptor downregulation cannot be excluded; however, if this adaptation occurred, the influence was overridden by a compensatory increase in sympathetic discharge.

Parasympathetic neural actions on HR include both direct and indirect effects on membrane electrical currents. The muscarinic effects of acetylcholine decrease HR directly by activating a slow inward sodium-potassium current (I_f) and indirectly by diminishing norepinephrine-induced activation of L-type calcium channels.^{9,24} In this study, the similar increases in HR from submaximal to maximal exercise in both control (11 bpm) and glycopyrrolate (13 bpm) trials at altitude suggest that cholinergic antagonism of sympathetic noradrenergic control of HR is not enhanced in chronic hypoxia. If this had been the case, we would have expected a smaller increase in HR from submaximal to maximal exercise in the control trial. Furthermore, altered vagal tone did not evoke compensatory changes in sympathetic neural outflow, as reflected by the similar catecholamine responses and leg vascular peripheral resistance and TPR at altitude with and without glycopyrrolate.

The second aim of this study was to determine the influence of parasympathetic activity on Q. It has been postulated that the marked reduction in peak HR after altitude acclimatization must contribute to lowering peak Q and therefore oxygen transport and physical work capacity.^{2,11} This study is the first to examine the role of the parasympathetic nervous system on both HR and Q after acclimatiza-

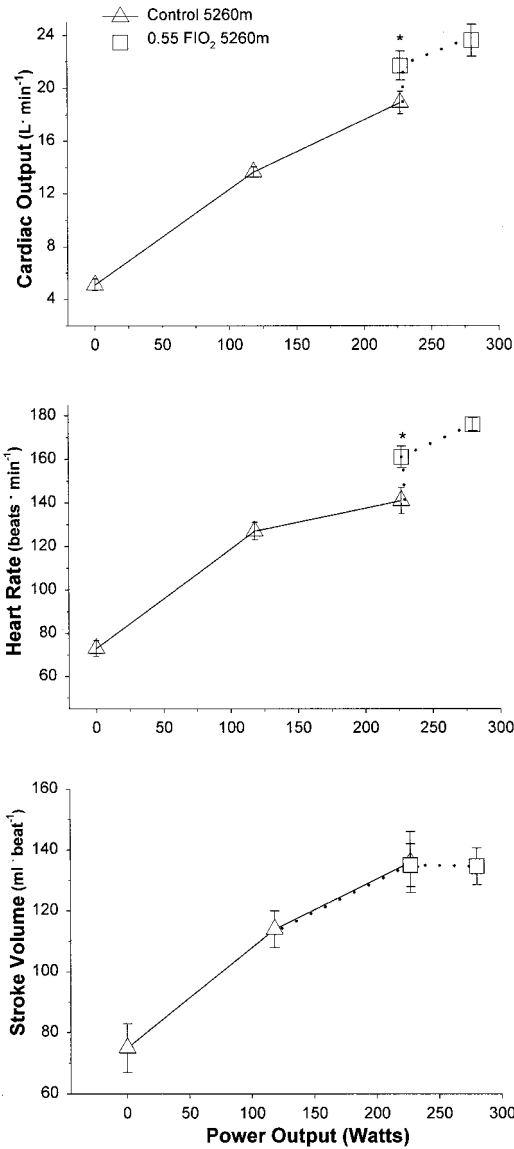


Figure 6. Influence of breathing 0.55 FiO_2 at peak exercise on maximal \dot{Q} , HR, and stroke volume after 9 weeks' acclimatization at 5260 m. Values are mean and SEM. *Significant effect of FiO_2 0.55, $P < 0.05$.

tion. An important finding was that parasympathetic blockade had no effect on \dot{Q} and O_2 transport at altitude. \dot{Q} , LBF, and leg and pulmonary $\dot{V}\text{O}_2$ were the same with and without glycopyrrolate at both submaximal and peak exercise. Despite a significantly higher HR with glycopyrrolate at altitude, stroke volume was reciprocally adjusted to maintain the same \dot{Q} . This finding suggests that the muscle pump and other mechanisms regulating cardiac filling ensure a rather constant venous return at a given work rate and that \dot{Q} can be maintained despite marked variations in HR. Moreover, because parasympathetic blockade fully restored maximal HR to the sea-level values without effect on maximal \dot{Q} , a major finding is that the lowering of HR with acclimatization does not limit O_2 transport and exercise performance at altitude. Thus, a limitation in stroke volume may account for the diminished peak \dot{Q} .¹⁴⁻¹⁷ The peak exercise \dot{Q} at altitude

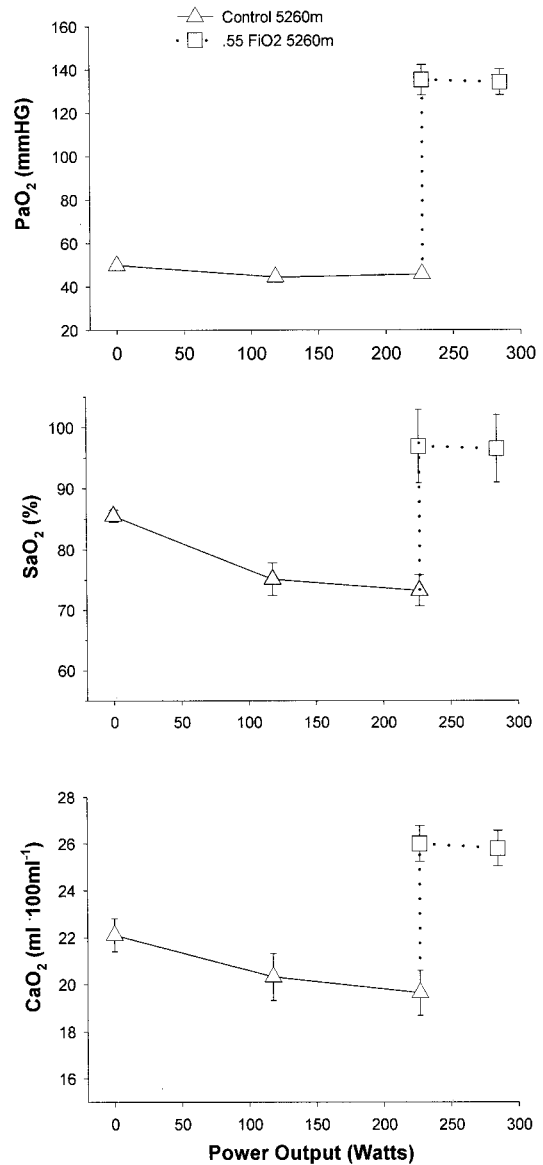


Figure 7. Arterial oxygen pressure (PaO_2), oxygen saturation (SaO_2), and arterial oxygen content (CaO_2) during control exercise at altitude and at peak exercise after breathing an oxygen-enriched gas mixture equivalent to sea level (FiO_2 0.55).

was ≈ 3.5 L/min lower than at sea level, and the corresponding stroke volume was 136 ± 10 mL, compared with 123 ± 7 mL during maximal exercise at sea level. When comparable peak HRs were achieved by parasympathetic blockade both at sea level (181 bpm) and at altitude (180 bpm), stroke volume was maintained at sea level but was reduced at altitude (from 136 to 102 mL). The finding that the heart was capable of delivering the largest stroke volume at altitude, however, suggests that ventricular performance is not impaired at altitude^{15,25-27} and does not limit \dot{Q} . The functional significance of increased parasympathetic activity at altitude may be to reduce myocardial oxygen demand at a given \dot{Q} and O_2 delivery, as has been proposed previously.²⁸ A comparison of the rate-pressure product (Figure 5) suggests that at altitude, enhanced vagal tone prevents increases in myocardial O_2 demand as systemic arterial pressure is elevated. The product

of HR and MAP, however, is only a rough estimate of myocardial O₂ demand. Accurate assessment of this parameter requires measurement of left ventricular end-diastolic volume and pressure.

The fact that stroke volume and HR can be manipulated markedly without influence on Q suggests that Q is the regulated variable, as demonstrated during exercise in individuals with pacemakers.²⁹ The consistency of the relationship between power output and Q at both sea level and altitude also suggests that these responses are closely interdependent. This is also supported by the finding that at altitude, peak Q and work capacity were both reduced by 20%. The mechanism for this coupling during dynamic exercise has not been clearly defined, but a prominent hypothesis is that as long as Q can be increased, muscle oxygen delivery will be sufficient to increase power output, which in turn will maintain ventricular filling by the muscle pump.³⁰

The mechanism underlying the reduction in peak Q at altitude remains to be resolved. In parallel experiments on this expedition, plasma volume expansion did not enhance peak Q, nor did hemodilution by venesection combined with dextran replacement. In all experiments, peak Q was the same, as was the SaO₂ at exhaustion. The progressive fall in arterial O₂ saturation and content as Q increased from rest to peak exercise suggests a pulmonary limitation in loading hemoglobin with oxygen. Given that pulmonary ventilation (and alveolar-capillary diffusion capacity) was already maximal, further increases in Q during exercise would most likely reduce SaO₂ to a level that would offset any benefit to systemic oxygen delivery; the SaO₂ (73%) was already on the steep position of the O₂ dissociation curve. Conversely, the recovery of Q to sea-level maximum values (Figure 6) with high FiO₂ (0.55) was coupled to increases in Pao₂ and SaO₂ (Figure 7). Thus, peak exercise Q at altitude is O₂-dependent. Mechanistically, Q can be blunted by direct hypoxic excitation of medullary neurons, which project to cardiovagal neurons, causing bradycardia.³¹ This response in turn would preserve an optimal match between erythrocyte transit time and pulmonary diffusion capacity so that the arterial O₂ saturation and tissue oxygen delivery are not compromised.

This study is the first to report an increase in peak Q to control sea-level values with relief of hypoxia in altitude-acclimatized individuals and is consistent with previous findings showing refractoriness of HR in lowlanders acclimatized to moderate altitude.² This response, however, is not evident in high-altitude residents,¹⁶ which probably reflects differences in long-term chemoreceptor adaptation to low PO₂. The observation that HR also rose abruptly with oxygen supplementation also reflects refractoriness of the chronotropic response of the heart when sea-level PO₂ is restored. This finding is not in discordance with previous studies demonstrating desensitization of the heart to sympathetic stimulation. No previous studies, however, have examined adrenergic responsiveness after acclimatization to high altitude with and without parasympathetic blockade. Adrenergic desensitization may occur as a response to diminish the effects of elevated sympathetic activation while preserving the ability to achieve maximal HR in the absence of vagal

activity. Also noteworthy is that stroke volume was maintained when HR was elevated by oxygen supplementation, providing further support to the conclusion that myocardial function is not impaired after altitude acclimatization. It remains to be determined what mechanism operates to rapidly restore HR and Q to maximal sea-level values in response to elevated PO₂.

Several factors should be considered in the interpretation of the present results. First, all subjects were well-trained and motivated exercise enthusiasts before participating in the high-altitude expedition. Second, during the 9-week sojourn at high altitude, all subjects were unrestricted in outdoor activity and maintained a high activity level through hiking, climbing, and cycling activity on a daily basis. In addition, they all participated in 2 separate 3-day expeditions to summits of 6100 and 6400 m, respectively, during their 9-week stay. Also, the subjects were extremely motivated during experimental sessions. These environmental conditions were probably factors contributing to the present experimental findings.

In summary, the results of this study demonstrate that the reduction in exercise HR after acclimatization to high altitude in healthy, active individuals is due to enhanced parasympathetic neural tone. In contrast to the sea-level response, vagal activity at altitude exerts control of HR from rest through maximal exercise. Yet, despite the pronounced vagal influence on HR, this adaptation does not account for the diminished Q at peak exercise in chronic hypoxia. The reduction of peak Q appears to be mediated by hypoxia, which may imply a role of medullary cardiovagal neurons. These findings may have important implications for interpreting autonomic control of the circulation in individuals with heart failure, pulmonary disease, or congenital heart defects who experience chronic hypoxemia.

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