O2 extraction maintains O2 uptake during submaximal exercise with β-adrenergic blockade at 4,300 m

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Wolfel, Eugene E., Mark A. Selland, A. Cymerman, George A. Brooks, Gail E. Butterfield, Robert S. Mazzeo, Robert F. Grover, and John T. Reeves. O2 extraction maintains O2 uptake during submaximal exercise with β-adrenergic blockade at 4,300 m. J. Appl. Physiol. 85(3): 1092–1102, 1998.—Whole body O2 uptake (VO2) during maximal and submaximal exercise has been shown to be preserved in the setting of β-adrenergic blockade at high altitude, despite marked reductions in heart rate during exercise. An increase in stroke volume at high altitude has been suggested as the mechanism that preserves systemic O2 delivery (blood flow × arterial O2 content) and thereby maintains VO2 at sea-level values. To test this hypothesis, we studied the effects of nonselective β-adrenergic blockade on submaximal exercise performance in 11 normal men (26 ± 1 yr) at sea level and on arrival and after 21 days at 4,300 m. Six subjects received propranolol (240 mg/day), and five subjects received placebo. At sea level, during submaximal exercise, cardiac output and O2 delivery were significantly lower in propranolol- than in placebo-treated subjects. Increases in stroke volume and O2 extraction were responsible for the maintenance of VO2. At 4,300 m, β-adrenergic blockade had no significant effect on VO2, ventilation, alveolar PO2, and arterial blood gases during submaximal exercise. Despite increases in stroke volume, cardiac output and thereby O2 delivery were still reduced in propranolol-treated subjects compared with subjects treated with placebo. Further reductions in already low levels of mixed venous O2 saturation were responsible for the maintenance of VO2 on arrival and after 21 days at 4,300 m in propranolol-treated subjects. Despite similar workloads and VO2, propranolol-treated subjects exercised at greater perceived intensity than subjects given placebo at 4,300 m. The values for mixed venous O2 saturation during submaximal exercise in propranolol-treated subjects at 4,300 m approached those reported at simulated altitudes >8,000 m. Thus β-adrenergic blockade at 4,300 m results in significant reduction in O2 delivery during submaximal exercise due to incomplete compensation by stroke volume for the reduction in exercise heart rate. Total body VO2 is maintained at a constant level by an interaction between mixed venous O2 saturation, the arterial O2-carrying capacity, and hemodynamics during exercise with acute and chronic hypoxia.

high altitude; oxygen transport

OXYGEN UPTAKE (VO2) during submaximal exercise is maintained over time at altitude because of a balance between O2 delivery and extraction. With acute hypoxia, cardiac output is maintained or increased in the setting of reduced arterial oxygenation. With adaptation to chronic hypoxia, arterial O2 saturation and hemoglobin concentration increase, while cardiac output usually falls to sea-level values or below, resulting in variable effects on O2 delivery (29, 35). A reduction in cardiac output with chronic hypoxia is not a consistent finding in studies performed at altitudes between 3,100 and 4,500 m (4, 7, 9, 29, 35) because of the variable responses in heart rate and stroke volume to high-altitude adaptation. Most studies, however, consistently report decreases in stroke volume during exercise, and the relationship between heart rate and stroke volume at high altitude determines the effect on cardiac output. Factors such as decreased cardiac preload and increased systemic vascular resistance with increased cardiac afterload may be responsible for the observed reductions in stroke volume. Sympathoadrenal activity, demonstrated by increased plasma catecholamine levels, is also enhanced at high altitude and may be responsible for some of the hemodynamic adaptations that occur during exercise with chronic high-altitude exposure (16). Increased activity of the β-adrenergic system can produce the increase in heart rate and metabolic rate seen at high altitude, whereas heightened α-adrenergic tone can produce the observed increases in systemic arterial pressure and resistance. Pharmacological blockade of the various limbs of the sympathetic nervous system might result in alterations in the hemodynamic adaptations to chronic hypoxia that would adversely affect exercise capacity at high altitude.

Previous studies at 4,300 m with propranolol, a nonselective β-adrenergic blocker, have shown no reductions in VO2 during submaximal and maximal exercise, despite significant reductions in exercise heart rate (20). A compensatory increase in stroke volume has been proposed as the mechanism for preserving cardiac output and thus O2 delivery. A related study in the same subjects suggested that cardiac output, measured noninvasively, was preserved at rest in the upright but not supine posture in subjects treated with propranolol after 15 days at 4,300 m (7). These data suggest a difference in the pattern of adaptation to chronic hypoxia between placebo-treated and β-blocked subjects. In these studies, propranolol had no effect on ventilatory acclimatization (21), suggesting that hemodynamic adaptations were responsible for the maintenance of VO2.
In the present study we tested the hypothesis that compensatory increases in stroke volume offset reductions in exercise heart rate produced by β-adrenergic blockade at high altitude, thereby maintaining cardiac output and systemic O₂ delivery at the same level observed in unblocked subjects. Thus exercise V˙O₂ should be preserved. Direct invasive hemodynamic measurements were made during exercise to determine the cardiac output response during submaximal exercise. O₂ delivery and extraction were also determined to investigate more completely the mechanism of maintenance of exercise V˙O₂ with β-adrenergic blockade at high altitude. In addition, we determined whether β-adrenergic blockade alters the typical hemodynamic adaptations seen with chronic hypoxia. These include a reduction in stroke volume, an increase in mean arterial blood pressure (MAP), and an increase in systemic vascular resistance. To our knowledge, this is the first study to employ direct hemodynamic measurements to determine the effects of β-adrenergic blockade on exercise responses in normal subjects during acute and chronic hypoxia.

METHODS

Eleven healthy male sea-level residents (26.7 ± 1.2 yr of age, 71.4 ± 3.2 kg body wt) participated in the study. All subjects were nonsmokers and were not involved in regular endurance exercise training. This project was approved by the institutional review boards of all the participating institutions, including the US Army Research Institute of Environmental Medicine. Subjects were randomly assigned to a control group (n = 5) receiving a placebo or to a β-blocked group (n = 6) receiving oral propranolol at 80 mg every 8 h. A daily propranolol dose of 240 mg/day has been shown previously to produce effective and safe β-adrenergic blockade in normal subjects at sea level and high altitude (20), and this was also confirmed in the present study as previously reported (17). The degree of β-adrenergic blockade was documented by monitoring the heart rate response to progressive increases in the intravenous dose of the β-adrenergic agonist isoproterenol. Administration of placebo or propranolol began at least 3 days before sea-level and altitude testing and continued for the entire 21 days at 4,300 m. This study was part of a larger project designed to examine the effects of β-adrenergic blockade on the metabolic and hemodynamic adaptations to chronic hypoxic exposure. The influences of β-blockade on sympathetic activity and metabolic function at 4,300 m have been previously reported (17–19, 27, 28).

Sea-level studies were performed in the Geriatrics Research, Education, and Clinical Center of the Palo Alto Veterans Affairs Health Care System, Palo Alto, CA [barometric pressure (Ps) 751 Torr, inspired P O₂ (Pi O₂) 148 Torr]. High-altitude studies were performed in the US Army Research Institute of Environmental Medicine's Maher Memorial Research Laboratory on the summit of Pikes Peak, CO (4,300 m, Ps 461–463 Torr, Pi O₂ 87 Torr). The initial altitude studies were performed ~4 wk after the sea-level studies. Subjects traveled by commercial air transport from California to Colorado, slept in Manitou Springs, CO (1,954 m) overnight, and then ascended Pikes Peak the next morning, within 24 h of leaving sea level. Subject arrival at altitude was staged so that all subjects were studied promptly on arrival and after an equivalent period of residence at altitude. To maximize the conditions of acute hypoxia on arrival at 4,300 m, all subjects rode by automobile to the summit of Pikes Peak while breathing supplemental O₂ to mimic sea-level values of arterial O₂ saturation (Sa O₂). Supplemental O₂ was discontinued on arrival at the Maher Memorial Laboratory. All altitude studies were performed within the first 4 h of arrival at 4,300 m and during 21 days of residence at the summit of Pikes Peak.

Food (30% fat, 58% carbohydrate, 12% protein, 4 g Na) and fluid intake were strictly controlled at sea level and 4,300 m to maintain nitrogen, energy, and fluid balances, thus avoiding fluctuations in body weight and lean body mass across experimental conditions as previously described (2). Mean subject body weight was unchanged throughout the study in both subject groups. The level of physical activity was also prescribed and maintained at a uniform, constant level at sea level and 4,300 m to avoid confounding effects of exercise training or deconditioning on the measured hemodynamic and ventilatory parameters.

Exercise protocols. Peak exercise O₂ consumption (V˙O₂ peak) was determined from a continuous progressive exercise protocol using an electrically braked cycle ergometer (Warren Collins) as previously described (17). The purpose of this maximal test was to determine the exercise intensity to be used during the steady-state submaximal invasive exercise test. Tests for the determination of V˙O₂ peak, were performed twice at sea level, once before and once after randomization to placebo or propranolol, and on days 4 and 19 of high-altitude exposure.Expired gas analysis and the determination of minute ventilation (VE) were performed using standard open-circuit techniques, with calibration adjusted for ambient conditions as previously described (17).

Submaximal exercise tests were performed at sea level and within 4 h of arrival (acute) and after 21 days of residence at 4,300 m (chronic). A submaximal workload was chosen to produce a V˙O₂ that approximated 50% of sea-level V˙O₂ peak. This same absolute workload was used for all steady-state exercise studies at sea level and high altitude. Because V˙O₂ peak did not change between days 4 and 19 of residence at altitude, this workload represented the same relative percent V˙O₂ peak for both studies at 4,300 m but was a higher relative workload than at sea level. Measurements were made while the subjects rested quietly in a sitting position for at least 90 min before the exercise test. Subjects then performed 45 min of upright cycle ergometry at the prescribed workload. Hemodynamic and respiratory measurements as well as blood samples were obtained at rest (15 and 0 min before exercise) and at 5, 15, 30, and 45 min of exercise. In the present report the exercise data represent a mean of the data obtained at 15, 30, and 45 min of exercise. Steady-state conditions were documented over this time period in each subject by observing no change in exercise V˙O₂ between 15 and 45 min of exercise. All subjects in both experimental groups were able to complete the 45 min of exercise at sea level and on arrival and after 21 days of residence at 4,300 m.

 Femoral arterial and venous catheterization. The femoral artery and vein were cannulated by standard percutaneous techniques as previously described (35). A 5-Fr, 50-cm catheter (Cordis aortic flush catheter) was positioned in the distal abdominal aorta, and a 6-Fr, 50-cm thermodilution venous catheter (model 93-135-6F, American Edwards Laboratories) was passed through a femoral vein sheath to position its tip in the distal iliac vein and proximal femoral vein ~13 cm from the skin to ensure as distal a position in the vein as possible. There were no significant complications from this procedure at sea level or at high altitude. The vessels were successfully cannulated in all subjects at all testing periods. Alternate legs were used in each testing period.

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Hemodynamic measurements. Heart rate was determined by single-lead electrocardiographic monitoring (model 8K22 recorder, Soltec, Sun Valley, CA). Distal abdominal aortic pressure was monitored at rest and throughout exercise with a fluid-filled transducer (model 23DB, Statham) calibrated to zero pressure at 5 cm below the sternal angle with phasic recordings on the Soltec recorder. Cardiac output was determined by the indicator-dilution technique using indocyanine green dye with a bolus injection of dye into the femoral vein and continuous sampling of femoral arterial blood through a spectrophotometric cell (D-402A densitometer and cuvette, Waters, Rochester, NY) to generate an indicator-dilution curve on the recorder. Cardiac output was determined using a standard indicator-dilution formula by the Hamilton method as previously described (35). Stroke volume was calculated by dividing cardiac output by heart rate. Systemic vascular resistance was determined by dividing MAP by cardiac output. Resistance values are expressed as dyn·s·cm⁻⁵. Leg blood flow was measured at rest and during exercise using the bolus thermodilution technique as previously described (35).

Blood-gas measurements. Arterial and leg venous blood samples were drawn simultaneously anaerobically over 5 s when V̇O₂ had reached a steady state at rest and at 5, 15, 30, and 45 min during exercise. The blood samples were immediately placed on ice and analyzed within 30 min for PₐO₂, PₐCO₂, and pH (ABL 300, Radiometer, Copenhagen, Denmark). O₂ content, O₂ saturation, and Hb concentration were measured independently in each blood sample (OSM3 hemoximeter, Radiometer), and arterial hematocrit (Hct) was determined by the microhematocrit method. The temperatures measured at the venous catheter tip thermistor were utilized to correct blood-gas tension to in vivo temperature. Alveolar PₐO₂ (PₐO₂) was calculated using the alveolar gas equation. Systemic arteriovenous O₂ difference was calculated from the Fick equation using the measured total body V̇O₂ from respiratory gas analysis and the cardiac output from the indocyanine green dye curves. Mixed venous O₂ saturation was also calculated by subtracting the arteriovenous O₂ difference from the measured arterial O₂ content (CaO₂ × 100) and dividing by Hb concentration × 1.34. Systemic O₂ delivery was the product of cardiac output and CaO₂. Systemic O₂ extraction (%) was obtained as follows: arteriovenous O₂ difference ÷ CaO₂ × 100. Leg V̇O₂ was calculated as directly measured leg blood flow × directly measured arteriovenous O₂ content difference across the leg at rest and during exercise.

Perceived exertion. Values for perceived exertion were obtained using a modified Borg scale (1 = very light, 3 = moderate, 5 = heavy, 7 = very heavy, 10 = maximal) at 5, 15, 30, and 45 min of exercise. Separate readings were obtained for total body exertion, leg fatigue, and breathlessness. The exercise values for each category were reported as the mean of the values at 15, 30, and 45 min of exercise.

Statistics. Values are means ± SE. Two-way ANOVA with Student-Newman-Keuls multiple-comparison testing was used to determine differences between the two subject groups across the three testing periods, sea level and acute and chronic hypoxia, using the SuperANOVA program (Abacus Concepts, Berkeley, CA). P < 0.05 was considered statistically significant.

RESULTS

Responses to isoproterenol. Propranolol-treated subjects challenged with intravenous isoproterenol showed a marked rightward shift in the dose-response curve for heart rate at sea level and at 4,300 m compared with placebo-treated subjects, suggesting a high degree of β-adrenergic blockade (Fig. 1). In placebo-treated subjects the slight rightward shift in the dose-response curve between sea level and 4,300 m was compatible with reduction in cardiac β-adrenergic receptor activity as has been previously reported (25, 33).

Resting hemodynamic and arterial blood-gas responses. At sea level, heart rate and cardiac output were lower in propranolol- than in placebo-treated subjects, but stroke volume was unchanged (Fig. 2). MAP was lower and systemic vascular resistance was higher with propranolol (Table 1). After arrival at 4,300 m, the propranolol-treated subjects displayed values similar to those at sea level, with lower heart rate, cardiac output, and MAP, unchanged stroke volume, and elevated systemic vascular resistance compared with placebo-treated subjects. After 21 days of residence at 4,300 m, stroke volume decreased in both groups, but cardiac output decreased only in the placebo-treated group. There were comparable increases in MAP and systemic vascular resistance in both groups (Table 1).

Arterial PₐCO₂ (PₐCO₂) was slightly lower in propranolol-treated subjects at sea level, while SₐO₂, CaO₂, arterial PₐO₂ (PₐO₂), pH, and Hb concentration (13.7 ± 0.1 vs. 14.0 ± 0.1 g in placebo- vs. propranolol-treated group) were not different between the groups (Table 1). A greater arteriovenous O₂ difference with propranolol but V̇O₂ similar to (290 ± 10 ml/min) placebo-treated
subjects \((320 \pm 40 \text{ ml/min, Table 1})\) resulted in the former group having a lower calculated mixed venous \(O_2\) saturation (Fig. 3). This lower calculated value of mixed venous \(O_2\) saturation in the propranolol-treated subjects was validated by a directly measured lower femoral venous \(O_2\) saturation (Fig. 3). Systemic \(O_2\) delivery was lower and systemic \(O_2\) extraction was greater in the propranolol-treated subjects (Fig. 4).

At 4,300 m, \(CaO_2\) was somewhat higher in propranolol-treated subjects, probably related to a somewhat greater \(Hb\) concentration, but \(SaO_2, P_aO_2, P_aCO_2,\) and \(pH\) were not different (Table 1). \(Hb\) concentrations for placebo- and propranolol-treated subjects on day 1 at 4,300 m were \(13.6 \pm 0.1\) and \(14.4 \pm 0.2\) g/100 ml, respectively. At day 21, \(Hb\) concentration rose to \(14.8 \pm 0.4\) and \(15.3 \pm 0.4\) g/100 ml in placebo- and propranolol-treated subjects, respectively. This represented 8.8 and 6.2% increases in placebo- and propranolol-treated subjects, respectively, as a result of acclimatization. The greater arteriovenous \(O_2\) differences in the propranolol-treated group resulted in a lower calculated mixed \(O_2\) saturation on day 1 and a trend toward a lower

Table 1. Resting hemodynamic and arterial blood responses at sea level and 4,300 m

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>Day 1</th>
<th>Day 21</th>
<th>Pikes Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Prop</td>
<td>Placebo</td>
<td>Prop</td>
</tr>
<tr>
<td>(\dot{V}O_2), ml/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole body</td>
<td>320 ± 40</td>
<td>290 ± 10</td>
<td>350 ± 20</td>
<td>300 ± 10†</td>
</tr>
<tr>
<td>Leg</td>
<td>20.9 ± 2.4</td>
<td>32.3 ± 3.4</td>
<td>22.3 ± 6.1</td>
<td>35.5 ± 7.0</td>
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<tr>
<td>Heart rate, beats/min</td>
<td>87 ± 9</td>
<td>57 ± 3†</td>
<td>91 ± 6</td>
<td>63 ± 3†‡</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>91 ± 3</td>
<td>82 ± 3†</td>
<td>84 ± 6</td>
<td>84 ± 3</td>
</tr>
<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>861 ± 70</td>
<td>1,316 ± 130†</td>
<td>812 ± 102</td>
<td>1,297 ± 99†</td>
</tr>
<tr>
<td>(SaO_2,%)</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
<td>79 ± 2*</td>
<td>79 ± 1*</td>
</tr>
<tr>
<td>(CaO_2,\text{vol}%)</td>
<td>18.5 ± 0.2</td>
<td>19.1 ± 0.2</td>
<td>14.9 ± 0.5*</td>
<td>15.8 ± 0.2†</td>
</tr>
<tr>
<td>(P_{aO_2},\text{Torr})</td>
<td>103 ± 3</td>
<td>105 ± 3</td>
<td>40 ± 2*</td>
<td>39 ± 1*</td>
</tr>
<tr>
<td>(P_{aCO_2},\text{Torr})</td>
<td>40 ± 1</td>
<td>37 ± 1†</td>
<td>29 ± 1*</td>
<td>30 ± 1*</td>
</tr>
<tr>
<td>(pH_3)</td>
<td>7.40 ± 0.01</td>
<td>7.41 ± 0.01</td>
<td>7.49 ± 0.01*</td>
<td>7.48 ± 0.01*</td>
</tr>
<tr>
<td>(CaO_2-CvO_2,\text{vol}%)</td>
<td>3.6 ± 0.3</td>
<td>5.9 ± 0.5†</td>
<td>4.0 ± 0.3</td>
<td>5.8 ± 0.4‡</td>
</tr>
</tbody>
</table>

Values are means ± SE. \(\dot{V}O_2, O_2\) uptake; MAP, mean arterial blood pressure; SVR, systemic vascular resistance; \(SaO_2,\) arterial \(O_2\) saturation; \(CaO_2,\) arterial \(O_2\) content; \(P_{aO_2},\) arterial \(P_{O_2}; P_{aCO_2},\) arterial \(P_{CO_2}; pH_3,\) arterial \(pH; CvO_2,\) venous \(O_2\) content; Prop, propranolol. Resting values are an average of 2 measurements obtained over a 15-min period. *P < 0.05 vs. sea level within subject group by ANOVA. †P < 0.05, placebo vs. propranolol by ANOVA. ‡P < 0.05, Pikes Peak day 1 vs. day 21 within subject group by ANOVA.
saturation on day 21 (Fig. 3). These changes in venous O₂ saturation were associated with directly measured lower femoral venous O₂ saturations in the propranolol-treated group (Fig. 3). Systemic O₂ delivery was lower and systemic O₂ extraction was greater in the propranolol-treated subjects at 4,300 m (Fig. 4). After 21 days at 4,300 m, resting total body V̇O₂ was greater than at sea level in both subject groups with no differences between the groups (Table 1). These systemic V̇O₂ changes at 4,300 m were not seen in the leg, where resting V̇O₂ was similar in both subject groups across all experimental conditions.

Exercise responses. V̇O₂peak and power output (W) were not different between the placebo- and propranolol-treated subjects at sea level or 4,300 m (17). The two groups had a comparable 22% reduction in V̇O₂peak and 24% reduction in power output at 4,300 m with no difference between the early and late altitude measurements in either group. As expected, the peak exercise heart rate response was lower at sea level and 4,300 m in propranolol- than in placebo-treated subjects.

Power output during submaximal exercise was maintained at a constant level at sea level and high altitude with a similar total body V̇O₂ in both groups (Table 2). V̇O₂ represented 48% of V̇O₂peak at sea level and ~65% at both time periods at 4,300 m in both subject groups. The ventilatory responses to acute and more chronic high-altitude exposures were similar in both groups.

During submaximal exercise at sea level the propranolol-treated subjects had lower heart rates (Table 3) and greater stroke volumes (Fig. 2); however, cardiac outputs (Fig. 2) remained lower than in placebo-treated subjects. Lower MAP and higher systemic vascular resistance were also seen with propranolol (Table 3). At 4,300 m, cardiac output remained lower with acute and chronic hypoxia in propranolol-treated subjects, despite larger stroke volumes. Adaptation to chronic hypoxia resulted in lower heart rate, stroke volume, and cardiac output in placebo-treated subjects (Fig. 2), while heart rate and cardiac output remained unchanged and stroke volume decreased by a smaller amount with propranolol. At 4,300 m, MAP and systemic vascular resistance behaved in a similar fashion in both subject groups.

At sea level, SaO₂, CaO₂, PAO₂, Pao₂, and Paco₂, and pH were not different between the groups. The wider arteriovenous O₂ differences in the propranolol-treated group reflected the lower calculated mixed venous and directly measured femoral venous O₂ saturations than in the placebo group (Fig. 3). Systemic O₂ delivery was lower and systemic O₂ extraction was greater in the propranolol-treated subjects (Fig. 4). At 4,300 m, Pao₂ was slightly lower with propranolol, whereas PAO₂, SaO₂, CaO₂, Pao₂, and pH were not different between the groups (Table 3). There were comparable increases in Hb concentration (8.8 and 6.2% with placebo and
propranolol) and \( \text{Sa}_O_2 \) (6.7 and 8.0% with placebo and propranolol), respectively, in both subject groups with acclimatization. The alveolar-arterial \( O_2 \) gradient decreased by 20% in both subject groups over 21 days at 4,300 m. The arteriovenous \( O_2 \) differences in the propranolol-treated group were even greater at 4,300 m than at sea level as a result of lower calculated mixed venous and directly measured femoral venous \( O_2 \) saturations (Fig. 3). Although \( O_2 \) delivery was lower and systemic \( O_2 \) extraction was greater in the propranolol-treated subjects at both high-altitude time points, there was some improvement in \( O_2 \) delivery with acclimatization (Fig. 4). Systemic as well as leg \( V_O_2 \) values were similar during exercise to that seen in placebo-treated subjects across all experimental conditions.

Perceived exertion. There were no differences in the perceived exertion values for total body exertion, leg fatigue, and breathing effort between the subject groups at sea level (Fig. 5). At the same exercise workload, but at a higher relative exercise intensity on arrival at 4,300 m, both groups demonstrated a significant increase in all parameters of perceived exertion. There was a tendency for a higher level of perceived exertion with propranolol than with placebo. With acclimatization there was a decrease in perceived exertion at the same absolute and relative exercise intensity in the placebo-treated group, but at levels still greater than at sea level. The decrease in perceived exertion with acclimatization was less in propranolol-treated subjects, especially with leg fatigue (Fig. 5B). Values for

### Table 2. Submaximal exercise responses at sea level and 4,300 m

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>Pikes Peak</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Prop</td>
</tr>
<tr>
<td>( V_O_2 ), l/min</td>
<td>1.56 ± 0.11</td>
<td>1.52 ± 0.07</td>
</tr>
<tr>
<td>( V_O_2\text{peak}, % )</td>
<td>47.7 ± 1.0</td>
<td>49.4 ± 2.1</td>
</tr>
<tr>
<td>Workload, W</td>
<td>88.6 ± 2.4</td>
<td>86.7 ± 3.1</td>
</tr>
<tr>
<td>( V_E ), l/min BTPS</td>
<td>40.2 ± 2.5</td>
<td>40.9 ± 1.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. Exercise responses are averages of data obtained at 15, 30, and 45 min of exercise. \( V_E \), minute ventilation; \( V_O_2\text{peak} \), peak \( V_O_2 \); *P < 0.05 vs. sea level. †P < 0.05 vs. Pikes Peak day 1.
Table 3. Hemodynamic and arterial blood responses during submaximal exercise at sea level and 4,300 m

<table>
<thead>
<tr>
<th></th>
<th>Sea Level</th>
<th>Day 1</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Prop</td>
<td>Placebo</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>150 ± 4</td>
<td>95 ± 5†</td>
<td>167 ± 6*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>99 ± 4</td>
<td>85 ± 3†</td>
<td>96 ± 3</td>
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<tr>
<td>SVR, dyn·s·cm⁻⁵</td>
<td>509 ± 10</td>
<td>579 ± 36†</td>
<td>463 ± 41</td>
</tr>
<tr>
<td>PAO₂, Torr</td>
<td>103 ± 1</td>
<td>106 ± 1</td>
<td>59 ± 1*</td>
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<td>SbO₂, %</td>
<td>97 ± 1</td>
<td>97 ± 1</td>
<td>77 ± 1*</td>
</tr>
<tr>
<td>CaO₂, ml/min</td>
<td>39 ± 1</td>
<td>38 ± 1</td>
<td>42 ± 1*</td>
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<tr>
<td>pH₆</td>
<td>7.38 ± 0.01</td>
<td>7.38 ± 0.01</td>
<td>7.42 ± 0.01*</td>
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<tr>
<td>Leg VO₂, ml/min</td>
<td>450 ± 21</td>
<td>500 ± 18</td>
<td>446 ± 29</td>
</tr>
<tr>
<td>Cao₂ - Cvo₂, vol%</td>
<td>9.9 ± 0.4</td>
<td>12.8 ± 0.5†</td>
<td>10.4 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. PAO₂, alveolar PO₂. Exercise values are averages of values obtained at 15, 30, and 45 min of submaximal exercise. *P < 0.05 vs. sea level within subject group by ANOVA. †P < 0.05, placebo vs. propranolol by ANOVA. ‡P < 0.05, Pikes Peak day 1 vs. day 21 within subject group by ANOVA.

perceived exertion were higher in propranolol- than in placebo-treated subjects after 21 days at 4,300 m for total body exertion and leg fatigue (P < 0.05) and tended to be higher for breathing effort.

DISCUSSION

The major finding in this study was that increased O₂ extraction, and not preserved cardiac output, was responsible for the maintenance of VO₂ during submaximal exercise in the presence of β-adrenergic blockade at 4,300 m. Although the exercise stroke volume response was greater in the propranolol- than in the placebo-treated group at sea level and at both time points at high altitude, this response alone was not sufficient to compensate for the reduction in exercise heart rate produced by β-adrenergic blockade. Thus cardiac output and, thereby, systemic O₂ delivery were reduced at 4,300 m with propranolol.

The validity of these findings is dependent on the adequacy of β-adrenergic blockade produced by the dose of propranolol in this study. A direct pharmacological challenge test with isoproterenol at sea level and 4,300 m demonstrated a >1 log reduction in the heart rate-agonist dose response, indicating a high degree of β-adrenergic blockade. In addition, there appeared to be a more pronounced degree of β-adrenergic blockade at 4,300 m than at sea level, suggesting that less propranolol was required at high altitude to produce the same degree of β-adrenergic blockade observed at sea level (15). These pharmacological data, along with the marked reductions in submaximal and peak exercise heart rates, confirmed a high degree of β-adrenergic blockade in our propranolol-treated subjects and indicated that our hypothesis could be adequately tested.

The lower resting and exercise heart rates with β-adrenergic blockade were consistent with prior studies at sea level (3, 5, 6, 11, 12, 14, 22, 24, 31, 32, 34, 35) and during acute and chronic hypoxia (7, 20, 26). Because heart rate was decreased with propranolol at 4,300 m and peak and submaximal exercise VO₂ were preserved at the same level as in placebo-treated subjects, VO₂ must have been maintained by a compensatory increase in stroke volume and/or an increase in the arteriovenous O₂ difference. Conflicting studies at sea level support a preserved cardiac output secondary to enhanced stroke volume (1, 11, 34) or a reduction in cardiac output with an increase in O₂ extraction (3, 6, 22, 23). With chronic hypoxic exposure at high altitude, stroke volume during exercise has been shown to decline (29, 35), which could influence the ability of stroke volume to maintain cardiac output in the setting of β-adrenergic blockade at high altitude. Because of the already widened arteriovenous O₂ difference observed at high altitude as part of the acclimatization process (9, 29), it was believed that further widening with β-adrenergic blockade at high altitude would be unlikely.

In this study, stroke volume during exercise was greater at sea level and with acute and chronic hypoxia at 4,300 m in the propranolol-treated subjects. Even at sea level the augmented stroke volume response was still insufficient to maintain cardiac output at the same value as in placebo-treated subjects. Thus cardiac output was lower in β-blocked subjects. Our findings at sea level are in agreement with some (3, 5, 6, 22, 24) but not all previous sea-level studies (1, 11, 34) on the exercise hemodynamic responses to β-adrenergic blockade. The response of stroke volume during exercise to β-adrenergic blockade may depend on the relationship between diastolic pressure and volume in the right and left ventricle (23). If a plateau in this relationship has been achieved, then the Frank-Starling mechanism alone could not augment cardiac preload to a sufficient degree to maintain stroke volume and thereby cardiac output. A similar pressure-volume relationship may be operative in the response of stroke volume during exercise to chronic hypoxia, thereby explaining the variable responses in cardiac output reported in the literature. At 4,300 m, despite a greater stroke volume during exercise than with placebo, propranolol-treated subjects were unable to completely compensate for the drug-induced bradycardia. Although maintenance of an intact stroke volume response to exercise with enlarge-
ment of end-diastolic volume has been shown to occur in normal subjects at sea level after pharmacological autonomic blockade with a selective $\beta_1$-adrenergic blocker and atropine (13), this mechanism was suboptimal with nonselective $\beta$-adrenergic blockade at sea level and high altitude in this study.

At 4,300 m, cardiac output during exercise in placebo-treated subjects tended to increase on arrival and then fell by 16% after 21 days, a response previously observed during submaximal exercise at 4,300 m (35). This response was not seen in the $\beta$-blocked subjects between days 1 and 21 at 4,300 m. These differences in the exercise cardiac output responses over time at 4,300 m between the two subject groups cannot be explained by changes in stroke volume alone, since stroke volume decreased in both groups. Because the cardiac output during exercise with chronic hypoxia did not decrease in the propranolol-treated subjects, despite a reduction in stroke volume, the lack of a reduction in exercise heart rate must explain this observation. There was a 7% decrease in heart rate during submaximal exercise at the same workload in the placebo-treated group over time at 4,300 m but no change in exercise heart rate with propranolol. Spectral analysis of resting sympathetic and parasympathetic heart rate variability in these subjects indicated that when early and late days at 4,300 m were compared, the role of cardiac sympathetic nervous system activity decreased and parasympathetic activity increased for the placebo-treated group, but there were no such changes with propranolol (10). Propranolol may also have prevented the downregulation of cardiac $\beta$-receptors, previously shown to occur with chronic hypoxia (25, 33), thereby preserving exercise heart rate at the same level with acute and chronic hypoxia.

Although cardiac output during exercise was lower in propranolol-treated subjects at sea level and 4,300 m, $O_2$ delivery to tissues could be preserved if there were compensatory increases in arterial oxygenation. A slower pulmonary transit time secondary to a reduced cardiac output could result in correction of any potential pulmonary diffusion limitation that would inhibit arterial oxygenation at high altitude. This would be especially important on arrival at 4,300 m, inasmuch as ventilatory acclimatization and increases in blood Hb concentration would not yet have occurred. However, there were no differences in rest or exercise $SaO_2$ or $CaO_2$ between the two subject groups with acute or chronic hypoxia. Thus $O_2$ delivery during exercise was lower with propranolol than with placebo at sea level and both altitude time points. Despite the lower systemic $O_2$ delivery with propranolol at sea level, there was a further reduction on arrival at 4,300 m because of the decrease in $CaO_2$. After 21 days at 4,300 m, systemic $O_2$ delivery increased to a point between sea-level and arrival values in the propranolol-treated group because of increases in Hb concentration and $SaO_2$. $PAO_2$ increased to a similar extent and alveolar-arterial $O_2$ difference decreased in a similar fashion in both subject groups. $PaO_2$ was lower during exercise in the propranolol-treated group with acute and chronic hypoxia, most likely reflecting the very low values of mixed venous and directly measured femoral venous $PO_2$ values in blood returning to the lung for reoxygenation. The responses of $PCO_2$ and pH during exercise at sea level and acute and chronic hypoxia were similar in both subject groups and agree with previous data that demonstrated no effect of propranolol on exercise ventilation and ventilatory acclimatization to high altitude (21, 22).
Because systemic O$_2$ delivery was decreased at 4,300 m, exercise V\(\dot{O}_2\) could only have been maintained by an increase in systemic O$_2$ extraction. The systemic arteriovenous O$_2$ content difference during exercise was unchanged in the placebo-treated group between sea level and on arrival at 4,300 m secondary to the drop in SaO$_2$, as well as a fall from 48 ± 2 to 25 ± 2% in mixed venous O$_2$ saturation. With adaptation to chronic hypoxia at 4,300 m, the arteriovenous O$_2$ difference increased by 22% in the placebo-treated group, primarily as a result of the increase in CaO$_2$, from increases in plasma Hb concentration and SaO$_2$. This increase in CaO$_2$, offset the fall in cardiac output to maintain a similar systemic O$_2$ delivery as previously shown at this altitude (35). Mixed venous O$_2$ saturation remained at the arrival level, despite 21 days of exposure to this altitude. Systemic O$_2$ extraction, however, increased, inasmuch as mixed venous O$_2$ saturation was the same in the setting of an improved CaO$_2$. In the propranolol-treated group, enhanced tissue extraction compensated for the decrease in exercise O$_2$ delivery at sea level. This was manifested by a widened arteriovenous O$_2$ content difference, a lower level of mixed venous O$_2$ saturation, and a greater degree of systemic O$_2$ extraction. These parameters of increased tissue extraction of O$_2$ during exercise in the propranolol-treated group were similar to the enhanced responses seen with chronic hypoxia in placebo-treated subjects. Nevertheless, there was further enhanced systemic O$_2$ extraction to a dramatic degree with values of mixed venous O$_2$ saturation as low as 4–5% during exercise on arrival at 4,300 m in two of the six propranolol-treated subjects. These values are similar to those previously reported from the distal femoral vein in normal, unblocked subjects during exercise at 3,100 m (4). Despite the greater systemic O$_2$ extraction during exercise with propranolol, the pattern of response to acute and chronic hypoxia was similar to that of the placebo-treated subjects, albeit to a more profound extent. The only exception was the increase in mixed venous O$_2$ saturation with a resulting decrease in systemic O$_2$ extraction observed in propranolol-treated subjects between arrival and 21 days at 4,300 m. This correlated with the slight improvement in systemic O$_2$ delivery secondary to increases in arterial O$_2$-carrying capacity along with no significant change in cardiac output.

A unifying concept emerges from these findings. For a given level of V\(\dot{O}_2\), as the O$_2$ delivery falls, whether by stroke volume, heart rate, CaO$_2$, or some combination of them all; there is a compensatory response of mixed venous O$_2$ saturation, which can reach levels as low as 10%. There appears to be a preserved relationship between O$_2$ delivery and mixed venous O$_2$ saturation. With \(\beta\)-adrenergic blockade alone in normoxia, heart rate is depressed; thereby, stroke volume and mixed venous O$_2$ saturation must respond. With acute hypoxia in the absence of \(\beta\)-blockade, CaO$_2$ is depressed and heart rate, stroke volume, and mixed venous O$_2$ saturation must respond. Acute hypoxia and \(\beta\)-blockade result in depression of heart rate and CaO$_2$, so stroke volume and mixed venous O$_2$ saturation must respond. With chronic hypoxia, CaO$_2$ increases, thereby alleviating the need for further reduction in mixed venous O$_2$ saturation. \(\beta\)-Adrenergic blockade appears to influence the cardiac output response in this setting by allowing a slightly greater increase in O$_2$ delivery, thereby reducing the level of O$_2$ extraction and the level of mixed venous O$_2$ saturation.

Comparison of the present data on Pikes Peak with the invasive hemodynamic findings reported during submaximal exercise in the Operation Everest II project (30) shows that during exercise the mixed venous O$_2$ saturations in propranolol-treated subjects approach values obtained at simulated altitudes of >6,000 m (Fig. 6). The placebo-treated subjects exercising at ∼90 W in this study have mixed venous O$_2$ saturations that are midway between values obtained at 60 and 120 W in the Operation Everest II study (30), indicating a preserved relationship between inspired Po$_2$, and mixed venous O$_2$ saturation during exercise across a wide range of altitudes (Fig. 6). However, the mixed venous O$_2$ saturation on arrival at 4,300 m in the propranolol-treated subjects is similar to that obtained at 60 W (lower workload) at a simulated altitude of 8,848 m (summit of Mt. Everest). With 21 days of residence at 4,300 m, the mixed venous O$_2$ saturation at 90 W in propranolol-treated subjects increased somewhat but was still similar to values obtained at simulated altitudes >6,000 m. Compared with the Operation Everest II values, these data would suggest a lower physiological limit to mixed venous O$_2$ saturation and that compensatory increases in O$_2$ extraction could not occur at extreme altitudes with \(\beta\)-adrenergic blockade due to tissue hypoxia, resulting in reductions in exercise capacity and V\(\dot{O}_2\).

Despite the preservation of exercise V\(\dot{O}_2\) in the setting of \(\beta\)-adrenergic blockade at acute and chronic hypoxia, exercise performance remains a concern. Studies at sea level with \(\beta\)-blockers report a decrease in

![Fig. 6. Mixed venous O$_2$ saturations during submaximal exercise at 60 and 120 W at various inspired O$_2$ pressures (Po$_2$) in Operation Everest II (OE-II) study (30) compared with our values obtained on PP-1 and PP-21 (Po$_2$ = 87 Torr) in placebo- and propranolol-treated subjects during 90-W workloads.](image-url)
Effects of and spend variable periods of time at high altitude. It would be difficult to extrapolate these data to patients taking propranolol at high altitude. Thus, the greater perceived exertion was present with acute and chronic hypoxia, although symptoms improved in a fashion similar to that with placebo treatment after acclimatization to 4,300 m. The greater perceived exertion in the blockaded group may reflect greater tissue hypoxia, and our prolonged endurance performance could be adversely affected by propranolol at high altitude.

This study focused on the physiological effects of -adrenergic blockade on submaximal exercise responses in normal subjects. It would be difficult to extrapolate these data to patients taking -blockers for hypertension and coronary heart disease who travel and spend variable periods of time at high altitude. Effects of -adrenergic blockade on exercise performance, symptomatology, and physiological responses to high-altitude exposure in these patients can only be determined by further study.

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