Sympathetic restraint of muscle blood flow during hypoxic exercise

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Submitted 12 November 2008; accepted in final form 16 March 2009

Stickland MK, Smith CA, Soriano BJ, Dempsey JA. Sympathetic restraint of muscle blood flow during hypoxic exercise. Am J Physiol Regul Integr Comp Physiol 296: R1538–R1546, 2009. First published March 18, 2009; doi:10.1152/ajpregu.90918.2008.—Control of exercising muscle blood flow is a balance between local vasodilatory factors and the increase in global sympathetic vasoconstrictor outflow. Hypoxia has been shown to potentiate the sympathetic vasoconstrictor response to exercise, potentially limiting the increase in muscle blood flow. Accordingly, we investigated sympathetic restraint to exercising muscle during whole body exercise in hypoxia. Six dogs chronically instrumented with ascending aortic and hindlimb flow probes and a terminal aortic catheter were studied at rest and mild (2.5 miles/h (mph), 5% grade) and moderate (4.0 mph, 10% grade) exercise while breathing room air or hypoxia (PaO2 90–120 mmHg). Exercise significantly increased hindlimb blood flow (FlowL, 17%) and cardiac output (CO, 10%), while tail (CondT) and hindlimb (ConDL) conductance decreased (33% and 43%, respectively). In hypoxia, the increase in ConDL during moderate exercise was significantly greater than during mild exercise (43% vs. 33%). These findings indicate that the vascular response to endogenous norepinephrine release remains intact in hypoxia at rest (9). However, others have shown that the vascular response to exogenous norepinephrine, angiotensin, and lower-body negative pressure is reduced with hypoxia in resting humans (17, 18), suggesting hypoxia-induced functional sympatholysis, i.e., a reduced vasodilatory potential of skeletal muscle, we hypothesized that, to maintain arterial blood pressure, the magnitude of sympathetic restraint to exercising muscle blood flow would be higher in hypoxia compared with normoxia.

In hypoxic conditions, the muscle sympathetic nerve response to exercise is potentiated (42). This exaggerated sympathetic response during hypoxic exercise may be secondary to increased central command, additional feedback from muscle metaboreceptors, muscle mechanoreceptors (37), carotid chemoreceptors (45, 46), and or further resetting of arterial baroreceptors (15). Similar to the previous findings at rest, some have found that the vascular response to endogenous norepinephrine release in exercising muscle is maintained during hypoxic hand-grip exercise (53) while others have found evidence of greater exercise sympatholysis with hypoxia (17). More recently, Wilkins et al. (52) have shown that α-adrenergic receptor blockade results in more vasodilation during hypoxic hand-grip exercise compared with normoxic exercise. It remains unclear if the increased sympathetic response results in greater sympathetic restraint of exercising muscle blood flow during whole body exercise in hypoxia or, alternately, if functional sympatholysis limits the sympathetic restraint of exercising muscle blood flow.

Accordingly, the purpose of the present study was to examine sympathetic restraint to exercising muscle during whole body exercise in hypoxia. Because of the considerable muscle mass incorporated during whole body exercise, and the tremendous vasodilatory potential of skeletal muscle, we hypothesized that, to maintain arterial blood pressure, the magnitude of sympathetic restraint to exercising muscle blood flow would be higher in hypoxia compared with normoxia.

METHODS

Chronic Instrumentation

All surgical and experimental procedures were approved by the Institutional Animal Care and Use Committee at the University of Wisconsin-Madison and conducted in accordance with the American Physiological Society’s “Guiding Principles in the Care and Use of Animals.” Six female mixed-breed hound dogs weighing between 19 and 23 kg were trained to lie quietly on a bed and to run on a motorized treadmill [2.5 miles/h (mph) 5% grade and 4.0 mph 10% grade].

Address for reprint requests and other correspondence: M. Stickland, Division of Pulmonary Medicine, Dept. of Medicine, 2E4.42 Walter C Mackenzie, Health Sciences Centre, Univ. of Alberta, Edmonton, Alberta, Canada T6G 2B7 (e-mail: michael.stickland@ualberta.ca).
grade) while wearing a nonrebreathing flow-through mask. After training, two surgeries were required to instrument the dogs for study. Similar to previous studies from our laboratory (29, 45), the first surgery included the implantation of an ascending aortic flow probe (type 20A, 20 mm, n = 6; Transonic Systems, Ithaca, NY), terminal aortic flow probe (type 10A, 10 mm, n = 6; Transonic Systems), and either a mesenteric flow probe (type 1.5RB, 1.5 mm, n = 3; Transonic Systems) or renal flow probe (type 4.0RB, 4 mm, n = 2; Transonic Systems). During this surgery, an ovariectomy/hysterectomy was also performed in five dogs. The second surgery involved the implantation of a catheter placed in the terminal aorta via cannulation of a small side branch of the femoral artery. All cables and catheters were exteriorized on the back.

For both surgeries, anesthesia was induced using sodium pentothal (20 mg/kg), and a surgical plane of anesthesia was maintained using isoflurane (1–1.5%) and mechanical ventilation. Strict sterile techniques were used during all surgical procedures, and appropriate antibiotics and analgesics were used postoperatively. Dogs were given 2 wk to recover from surgery before data collection.

Experimental Protocol

Each animal performed the protocols described below over the course of a 2- to 3-wk period. For resting studies, dogs were placed on a padded bed in a sound-attenuated room, while exercise studies were performed on a motorized treadmill. Only one blockade experiment was conducted per day. All implanted instrumentation was connected, and each dog breathed through a nonrebreathing positive flow-through mask.

α1- and α2-Blockade

Rest. At rest, data collection began once a steady state in cardiac output was determined. Following 5 min of room-air breathing, hypoxia [target arterial partial pressure of O2 (PaO2) = 45 mmHg, fraction of inspired O2 (FIO2) = 0.11] was given for 5 min, followed by a second 5 min of room-air breathing. During steady-state conditions, phentolamine, an α1- and α2-blocker (2 mg/kg, dissolved in sterile saline and diluted to a concentration of 10 mg/ml), was administered via the terminal aortic catheter. Adrenergic blockade was confirmed by an absence of hindlimb vasoconstrictor response to a 25-μg intra-arterial injection (terminal aorta) of the α1-agonist phenylephrine (5). Following the attainment of a new steady state in the presence of blockade, data were collected again for 5 min of normoxia, 5 min of hypoxia, and 5 min of normoxia. α-Blockade was maintained with additional injections of phentolamine (0.5 mg/kg every 10 min), and confirmed at the end of each trial with a 25-μg intra-arterial injection of phenylephrine.

Exercise. To examine the exercise response to α-blockade with phentolamine, two protocols were conducted to reduce any order effect. In protocol A, each dog exercised at a fixed workload (either 2.5 mph 5% grade or 4.0 mph 10% grade), and FIO2 was altered (normoxia-hypoxia-normoxia) as described above. Phentolamine was then given, and FIO2 was altered again as described above. In protocol B, dogs breathed either normoxic or hypoxic gas throughout the entire experimental session. Dogs exercised at 2.5 mph 5% grade and then 4.0 mph 10% grade for 3–5 min each. Phentolamine was then given, and the graded exercise was repeated. As with the resting experiments, α-blockade was maintained with additional injections of phenylephrine (0.5 mg/kg every 10 min) and confirmed at the end of each trial with a 25-μg intra-arterial injection of phenylephrine.

Arterial Blood Gases

Arterial blood samples were obtained regularly both at rest and during exercise. Blood-gas measurements were analyzed in duplicate on an automated blood gas analyzer (Radiometer ABL-505) that was validated daily with tonometered blood. Samples were corrected for body temperature, and systematic error was determined by tonometry data.

<table>
<thead>
<tr>
<th>pH</th>
<th>Normoxia Rest</th>
<th>Normoxia 2.5 mph 5% Grade</th>
<th>Normoxia 4.0 mph 10% Grade</th>
<th>Hypoxia Rest</th>
<th>Hypoxia 2.5 mph 5% Grade</th>
<th>Hypoxia 4.0 mph 10% Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO2, mmHg</td>
<td>4.3</td>
<td>22</td>
<td>2.2</td>
<td>4.3</td>
<td>7.498</td>
<td>7.474</td>
</tr>
<tr>
<td>PO2, mmHg</td>
<td>92.0</td>
<td>99.1</td>
<td>105.2</td>
<td>35.8</td>
<td>34.1</td>
<td>32.2</td>
</tr>
<tr>
<td>[HCO3]</td>
<td>18.3</td>
<td>20.9</td>
<td>20.2</td>
<td>1.9</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>P0.1, mmHg</td>
<td>3.7</td>
<td>0.9</td>
<td>1.0</td>
<td>3.7</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

PCO2, partial pressure of CO2; PO2, partial pressure of O2; [HCO3], HCO3 concentration. P < 0.05 vs. normoxia (*), hypoxia (†), and normoxia blockade (‡).
Data Analysis

All signals were digitized and stored on the hard drive of a personal computer for subsequent analysis and on a polygraph (K2G; AstroMed, West Warwick, RI). All blood flow and blood pressure data were analyzed on a beat-by-beat basis using custom analysis software developed in our laboratory. Total, hindlimb, mesenteric, and renal conductance were calculated as follows: flow (ml/min)/mean arterial pressure (mmHg). Mesenteric and renal data were combined and reported as visceral blood flow/conductance. Hemoglobin saturation was calculated from blood gas data and temperature (43). Arterial oxygen content was calculated based on the regression equation for hemoglobin concentration during incremental exercise developed by Hsia et al. (20), assuming little change with acute hypoxia (49). Group data for each variable are expressed as means ± SE.

To evaluate the responses to hypoxia/phentolamine, beat-by-beat steady-state data from the last 2–3 min of each condition were averaged. No consistent difference was observed between the steady-state responses in exercise protocol A vs. B; therefore, the mean of both protocols was used for each dog. For the prazosin infusions, the peak single beat cardiovascular response within 20 s of infusion plus the two preceding and two subsequent beats (i.e., a 5-beat average) were compared with baseline values obtained in the preceding 30-s control condition. Our main findings were the same whether the peak three, five, or seven heart beat changes were used.

Statistics

For all inferential analyses, the probability of type I error was set at 0.05. Within each workload (rest, 2.5 mph 5% grade, 4.0 mph 10% grade), steady-state data between each condition (normoxia, hypoxia, normoxia blockade, hypoxia blockade) were evaluated with one-way repeated-measures ANOVA. Upon detection of an effect, paired t-test comparisons were made, and a Bonferroni correction factor was applied to maintain family-wise error rate at 0.05.

RESULTS

Rest

Blood gas data are reported in Table 1, whereas resting cardiovascular data are reported in Table 2. Hypoxia significantly reduced PaO2, and increased ventilation relative to normoxia, as evidenced by a reduction in arterial partial pressure of CO2. Hindlimb flow and cardiac output were increased with hypoxia; thus, O2 delivery was maintained, with the increase in cardiac output accomplished by elevated heart rate. Conductance was unaffected by hypoxia (see Fig. 3 and Table 2), but an increase in blood pressure was observed.

\( \alpha \)-Adrenergic blockade increased cardiac output, hindlimb flow, and total and hindlimb conductance both in normoxia and hypoxia, with the magnitude of the change in conductance greater in hypoxia. The increase in cardiac output and hindlimb flow following \( \alpha \)-blockade increased O2 delivery both in normoxia and hypoxia. Blood pressure was reduced in both conditions relative to the control intact condition.

Mild Exercise: 2.5 mph, 5% Grade

Figure 1 shows a representative trace of the steady-state response to a step change in FIO2 during mild exercise. Figure 2 is a representative trace from one dog performing graded exercise on two separate days with and without adrenergic blockade, day 1 in normoxia and day 2 hypoxia. See Fig. 3 and Table 3 for mean cardiovascular data.

![Fig. 1. Steady-state response during mild exercise (2.5 mph, 5% grade) while breathing normoxia and hypoxia.](http://ajpregu.physiology.org/)

<table>
<thead>
<tr>
<th>Table 2. Resting steady-state cardiovascular data in normoxia and hypoxia with and without ( \alpha )-adrenergic blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia</td>
</tr>
<tr>
<td>Cardiac output, l/min</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
</tr>
<tr>
<td>Hindlimb flow, l/min</td>
</tr>
<tr>
<td>Visceral flow, ml/min</td>
</tr>
<tr>
<td>Visceral conductance</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
</tr>
<tr>
<td>Systemic O2 delivery, l/min</td>
</tr>
<tr>
<td>Hindlimb O2 delivery, l/min</td>
</tr>
</tbody>
</table>

\( P < 0.05 \) vs. normoxia (*), hypoxia (†), and normoxia blockade (‡).
During mild exercise, hypoxia increased hindlimb flow, cardiac output, and blood pressure; however, both total and hindlimb conductance were unchanged. Despite the increase in cardiac output and hindlimb flow, both total and leg O2 delivery were reduced with hypoxia. Compared with the intact condition, H9251-blockade increased cardiac output, hindlimb flow, and total and hindlimb conductance both in normoxia and hypoxia, with the magnitude of the change in conductance greater in hypoxia. Blood pressure was reduced substantially in both conditions relative to control. As a result of the increase in cardiac output and hindlimb flow, total and hindlimb O2 delivery were increased following H9251-blockade relative to the respective control intact condition. At both FIO2 values, there was a greater proportional increase in hindlimb conductance compared with total conductance following H9251-blockade, indicating that H9251-blockade resulted in increased blood flow distribution to exercising muscle (see Fig. 4).

**Moderate Exercise: 4.0 mph, 10% Grade**

Compared with normoxia, hypoxia resulted in an increase in cardiac output, hindlimb flow, and blood pressure (Table 4 and Fig. 3). Unlike mild-intensity exercise, total and hindlimb conductance were increased with hypoxia. Total O2 delivery was reduced with hypoxia; however, hindlimb O2 delivery was maintained because of the greater proportional increase in hindlimb conductance.

α-Blockade resulted in substantial increases in cardiac output, hindlimb flow, as well as total and hindlimb conductance both in normoxia and hypoxia. Both systemic and hindlimb O2 delivery were increased following α-blockade in normoxia. In hypoxia, systemic O2 delivery was increased relative to the control intact condition, although hindlimb O2 delivery was not. At both FIO2 values, stroke volume dropped with blockade despite increased cardiac output. Adrenergic blockade substantially reduced blood pressure in both conditions, with the percent change much greater in hypoxia.

**α1-Receptor Blockade: 2.5 mph, 5% Grade**

The cardiovascular response to intra-arterial injection of prazosin is detailed in Table 5, with the peak change in hindlimb conductance illustrated in Fig. 5. Infusions of prazosin increased hindlimb flow and conductance, with the magnitude of the vasodilatory response similar
in normoxia compared with hypoxia. Cardiac output and total conductance were also slightly increased with prazosin while blood pressure was decreased.

**DISCUSSION**

The purpose of the present study was to determine the effects of hypoxia on sympathetic-mediated restraint of vascular conductance in exercising limb muscle. α-Adrenergic blockade with phentolamine resulted in significant increases in total and hindlimb conductance and systemic hypotension both at rest and during light- and especially moderate-intensity exercise. The increase in conductance with α-blockade was significantly greater in hypoxia compared with normoxia both at rest and during exercise. Likewise, selective α1-receptor blockade with prazosin during exercise also demonstrated significant vasodilation in hypoxia as well as with normoxia. These results indicate that, consistent with recent work exercising a small muscle mass in humans (52), considerable sympathetic restraint of muscle blood flow occurs during whole body exercise in hypoxia. Thus our findings demonstrate significant vasodilatory reserve in hypoxic exercising muscle and are consistent with earlier predictions by Rowell and Blackmon (35) indicating that sympathetic vasoconstrictor outflow to exercising skeletal muscle must be augmented even further in hypoxia to maintain blood pressure because of the additional local vasodilatory influences produced in hypoxia.

**Rest**

Hypoxia increases sympathetic nervous activity (2, 14, 16, 36, 42, 48) secondary to carotid chemoreceptor stimulation (2, 14). At the same time, factors facilitating local vasodilation with hypoxia may include direct prostaglandin (28) or nitric oxide (NO) formation (31), release of NO from the hemoglobin molecule in response to off loading of oxygen from hemoglobin (27, 44), the promotion of prostaglandin formation secondary to increased adenosine (32), and increased arterial ATP secondary to hemoglobin deoxygenation (12). In the present study, cardiac output, hindlimb flow, and blood pressure were increased with hypoxia, whereas total and hindlimb conductance were unchanged. These results indicate that any increase in local vasodilation with hypoxia was offset by the increased sympathetic vasoconstrictor outflow with hypoxia such that net vascular conductance was unchanged. Previous studies in anesthetized (1, 4) and awake sedated (10) dogs have also shown a hypertensive response to hypoxia, and, when conductance is calculated from published cardiovascular data (1), total conductance appears to be unchanged with hypoxia. Of note, milder hypoxia (PaO₂ = 53 mmHg) has not been found to cause hypertension in resting dogs (3). The observation that hypertension occurs in dogs exposed to significant hypoxia (i.e., PaO₂ < 50 mmHg) is in contrast to human (9, 18, 51, 53) and rat (26) studies that typically demonstrate a net vasodilatory response to hypoxia (see comments below regarding species differences).

α-Blockade increased total and hindlimb conductance both in normoxia and hypoxia. The magnitude of the change in

### Table 3. Mild exercise (2.5 mph, 5% grade) steady-state cardiovascular data in normoxia and hypoxia with and without α-adrenergic blockade

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia</th>
<th>Normoxia α-blockade</th>
<th>Hypoxia α-blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac output, l/min</td>
<td>6.65</td>
<td>7.46*</td>
<td>7.20*</td>
<td>7.69‡</td>
</tr>
<tr>
<td></td>
<td>0.31</td>
<td>0.20</td>
<td>0.37</td>
<td>0.33</td>
</tr>
<tr>
<td>Stroke volume, ml</td>
<td>43.4</td>
<td>42.9</td>
<td>33.7*</td>
<td>34.4†</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>1.9</td>
<td>0.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>154</td>
<td>176*</td>
<td>214*</td>
<td>225†</td>
</tr>
<tr>
<td>Hindlimb flow, l/min</td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>1.62</td>
<td>1.83*</td>
<td>1.93*</td>
<td>2.20‡</td>
</tr>
<tr>
<td>(L/min)</td>
<td>0.17</td>
<td>0.17</td>
<td>0.22</td>
<td>0.24</td>
</tr>
<tr>
<td>Visceral flow, ml/min</td>
<td>50.3</td>
<td>42.2</td>
<td>42.5</td>
<td>40.9</td>
</tr>
<tr>
<td></td>
<td>22.1</td>
<td>22.6</td>
<td>21.3</td>
<td>22.7</td>
</tr>
<tr>
<td>Visceral conductance</td>
<td>0.57</td>
<td>0.45</td>
<td>0.57</td>
<td>0.60‡</td>
</tr>
<tr>
<td></td>
<td>0.28</td>
<td>0.27</td>
<td>0.31</td>
<td>0.35</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>97.9</td>
<td>106.2*</td>
<td>79.9*</td>
<td>70.6‡</td>
</tr>
<tr>
<td></td>
<td>5.4</td>
<td>7.0</td>
<td>3.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Systemic O₂ delivery, l/min</td>
<td>1.38</td>
<td>1.22*</td>
<td>1.52*</td>
<td>1.28‡</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.03</td>
<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Hindlimb O₂ delivery, l/min</td>
<td>0.34</td>
<td>0.30*</td>
<td>0.41*</td>
<td>0.37†</td>
</tr>
<tr>
<td></td>
<td>0.04</td>
<td>0.03</td>
<td>0.05</td>
<td>0.04</td>
</tr>
</tbody>
</table>

mph, Miles/h. P < 0.05 vs. normoxia(*), hypoxia (†), and normoxia blockade (‡).
conductance was greater in hypoxia, indicating greater sympathetic restraint with hypoxia. These findings are consistent with previous human work in the forearm showing that the activation of sympathetic vasoconstrictor outflow with hypoxia greatly limits the vasodilatory response to hypoxia (51).

Exercise

Seals et al. (42) have shown that the sympathetic response to exercise is greater in hypoxia than it is in normoxia. Possible mechanisms for this exaggerated sympathetic response to hypoxic exercise include elevated central command, additional feedback from muscle metaboreceptors and/or muscle mechanoreceptors (37), further resetting of arterial baroreceptors (15), and increased feedback from carotid chemoreceptors (45, 46). We propose that the increased sympathetic response during hypoxic exercise is mediated chiefly by the carotid chemoreceptor, since 1) the carotid chemoreceptor contributes to sympathetic vasoconstrictor outflow during exercise (46, 47);

2) the carotid chemoreceptor is the primary hypoxia sensor and carotid chemoreceptor stimulation causes increases in sympathetic vasoconstrictor outflow (14); and 3) similar to the muscle sympathetic nerve activity response detailed by Seals et al. (42), the ventilatory response to hypoxia is greatly potentiated with exercise (50). However, our study does not rule out contributions from other mechanisms cited above, and further work will be required to establish whether or not there is a role for any of these mechanisms.

In the current study, conductance was unchanged with hypoxia during mild-intensity exercise but was elevated above normoxic values during moderate-intensity exercise in hypoxia. Sympathetic nervous activity increases with exercise intensity (40, 41), whereas at the same time a decrease in the relative effects of sympathetic restraint on exercising muscle blood flow has been shown with increasing exercise intensity (5). In hypoxia, as exercise intensity increases, we would expect even greater sympathetic vasoconstrictor outflow cond-
comitant with greater sympatholysis secondary to greater local metabolite production. Our findings indicate that, during mild exercise, there is a balance of vasodilatory mediators from hypoxia vs. global sympathetic vasoconstrictor outflow, whereas, during higher-intensity exercise, the net effect was vasodilation. Despite the net vasodilatory response during higher-intensity hypoxic vs. normoxic exercise, sympathetic blockade demonstrated that substantial sympathetic restraint of exercising muscle blood flow remained.

Our results are consistent with recent human work showing a vasodilatory reserve during hypoxic exercise (25) that can be induced by ATP infusion (25) and/or α-adrenergic blockade (52). Recent work (52) indicates that β-adrenergic stimulation may also contribute to the vasodilation during hypoxic exercise, since β-blockade with propranolol in combination with phentolamine (i.e., α-and β-blockade) resulted in less of an increase in forearm blood flow and conductance compared with phentolamine alone (i.e., α-blockade alone). However, interpretation of these data (52) is somewhat difficult, since baseline heart rate appears slighter lower with α- and β-blockade compared with α-blockade alone, suggesting a reduction in cardiac output may have occurred with β-blockade.

Thus, despite the release of well-established vasodilators with hypoxia, considerable sympathetic restraint to exercising muscle blood flow is also present with hypoxic exercise, which appears to intensify with increasing exercise intensity.

**Blood Flow Distribution**

α-Adrenergic blockade caused a greater proportional increase in hindlimb conductance compared with total conductance during mild normoxic and hypoxic exercise, as well as during moderate normoxic exercise. However, visceral blood flow was only modestly affected with α-blockade compared with total conductance. This is perhaps not surprising since greater sympathetic outflow is required to be directed at working muscle during exercise to maintain blood pressure (37). Previous studies with α-blockade in hypoxia have also observed no change in proportional blood flow to the kidneys, stomach, or intestines (10). This finding is also consistent with our previous findings that the reduction in sympathetic vasoconstrictor outflow during exercise via carotid chemoreceptor inhibition results in greater vasodilation in the hindlimb compared with the mesenteric artery (45). Likewise, Rutherford and Vatner (39) found greater carotid chemoreceptor-induced sympathetic vasoconstriction in the iliac artery (i.e., blood flow to muscle) compared with the mesenteric vascular bed (39). Combined, these results indicate that the visceral vasculature is relatively less sensitive to α-adrenergic modulation compared with skeletal muscle vasculature at rest and during exercise.

**Methodological Considerations**

**Sympathetic blockade.** In the present study, phentolamine was used to block both α₁- and α₂-receptors. The effect of blocking α₂-receptors is to elevate circulating catecholamines, which in the presence of α₁-receptor blockade will exert a β-adrenergic effect on the heart (19, 23). We did observe an increase in heart rate with phentolamine but did not see any consistent effect on stroke volume. A more likely explanation for our observed increase in heart rate with phentolamine is from baroreceptor stimulation secondary to systemic hypotension. Importantly, both cardiac output and hindlimb flow were measured, allowing for differentiation between the central cardiac vs. the local vasodilatory effect of α-blockade. Furthermore, the transient response to α₁-blockade with prazosin also showed substantial sympathetic restraint of exercising muscle blood flow with hypoxia, supporting our steady-state findings of significant sympathetic restraint of exercising muscle blood flow during exercise in hypoxia. Of note, specific α₂-blockade studies were not performed in the present study; therefore, the relative contribution of α₂-receptors to the sympathetic constraint of muscle during whole body hypoxic exercise is unclear.

**Hormonal effects.** As detailed in METHODS, an ovariectomy/hysterectomy was performed in five of the six dogs; thus, these dogs were deficient in circulating estrogen. Estrogen can modulate vascular tone through direct effects on endothelial function (30); importantly, however, the vasoconstrictor response to phenylephrine or norepinephrine does not appear to be affected by estrogen (8, 24). In the current study, there was no apparent difference between the intact dog vs. the ovariectomy/hysterectomy group, since the intact dog data were always within one standard deviation of the group data in all conditions, suggesting that the lack of estrogen did not influence conductance.
Vascular Regulation in Dogs

The dog model was selected for the current study because of the ability to measure multiple vascular beds during whole body exercise. Furthermore, the considerable hypotension observed following α-blockade during exercise would have prohibited the study of humans using a similar intervention during upright whole body exercise. In contrast to our findings at rest and during mild exercise, humans typically demonstrate vasodilation with hypoxia both at rest (9, 18, 51, 53) and during submaximal exercise (6, 13, 22, 38). Unlike other mammals, the dog does not release ATP from the red blood cell with a drop in oxygenation (11). ATP is a potent vasodilator (7, 12, 34) and has even been shown to override α-adrenergic vasoconstrictor outflow from tyramine to produce vasodilation in the leg (34). The lack of release of ATP from the red blood cell with hypoxia in the dog may explain why we did not observe an increase in conductance with acute hypoxia at rest or during mild exercise; however, we did observe a net vasodilation with hypoxia at the higher exercise workload.

Perspectives and Significance

The present study examined sympathetic restraint to exercising muscle blood flow in acute hypoxia. Consistent with previous predictions (35), greater sympathetic restraint of exercising muscle blood flow occurred during whole body exercise in hypoxia compared with normoxia. This increased vasoconstrictor outflow in hypoxia is vital to counterbalance the vasodilatory mediators produced with hypoxia so that arterial blood pressure can be maintained during exercise.

ACKNOWLEDGMENTS

We thank Kathy Henderson, Dr. Juan Carlos Robles, and Adrian Tabares for assistance.

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