Sympathetic vasoconstriction in active skeletal muscles during dynamic exercise

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Buckwalter, John B., Patrick J. Mueller, and Philip S. Clifford. Sympathetic vasoconstriction in active skeletal muscles during dynamic exercise. J. Appl. Physiol. 83(5): 1575–1580, 1997.—Studies utilizing systemic administration of \( \alpha \)-adrenergic antagonists have failed to demonstrate sympathetic vasoconstriction in working muscles during dynamic exercise. The purpose of this study was to examine the existence of active sympathetic vasoconstriction in working skeletal muscles by using selective intra-arterial blockade. Six mongrel dogs were instrumented chronically with flow probes on the external iliac arteries of both hindlimbs and with a catheter in one femoral artery. All dogs ran on a motorized treadmill at three intensities on separate days. After 2 min, the selective \( \alpha_1 \)-adrenergic antagonist prazosin (0.1 mg) was infused as a bolus into the femoral artery catheter. At mild, moderate, and heavy workloads, there were immediate increases in iliac conductance of 76 ± 7, 54 ± 11, and 22 ± 6% (mean ± SE), respectively. Systemic blood pressure and blood flow in the contralateral iliac artery were unaffected. These results demonstrate that there is sympathetic vasoconstriction in active skeletal muscles even at high exercise intensities.

blood flow; \( \alpha \)-adrenergic receptor; autonomic nervous system; prazosin; dogs

AT THE ONSET of dynamic exercise, the body is challenged to meet an increase in oxygen consumption in contracting skeletal muscle. This challenge is met with a redistribution of cardiac output away from inactive tissue to exercising skeletal muscle (2). The role of the autonomic nervous system in control of blood flow to active skeletal muscle is not fully understood. There is evidence for an increase in sympathetic nerve activity to active skeletal muscle during exercise (3, 18, 23) and that sympathetic nerve activity increases further during more intense exercise (3). However, whether this sympathetic activity reduces blood flow to exercising skeletal muscles is controversial. Several studies have provided evidence for sympathetic restraint of blood flow to active skeletal muscle (8, 19, 25) whereas others have not seen such an effect (4, 5, 10, 12).

This study examined the existence of active sympathetic vasoconstriction in dynamically exercising skeletal muscle and the relationship of sympathetic vasoconstriction with exercise intensity. We used a unique experimental approach that allowed examination of sympathetic control of blood flow to one hindlimb while not affecting systemic hemodynamics in conscious, exercising dogs. We hypothesized that there is sympathetic vasoconstriction in dynamically exercising skeletal muscle. Additionally, because there is competition between sympathetic vasoconstriction and metabolic vasodilation, we hypothesized that the magnitude of sympathetic vasoconstriction would decrease as exercise intensity increased.

METHODS AND PROCEDURES

All experimental procedures were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with the American Physiological Society’s “Guiding Principles in the Care and Use of Animals.” Six mongrel dogs, weighing 20–24 kg and selected for their willingness to run on a motorized treadmill, were instrumented in a series of sterile surgical procedures. Anesthesia was induced with thiopental sodium (15–30 mg/kg; Gensta Pharmaceuticals, Irvine, CA). After dogs were intubated with a cuffed endotracheal tube, a surgical level of anesthesia was maintained through mechanical ventilation with 1.5% halothane (Halocarbon Laboratories, River Edge, NJ) and 98.5% oxygen. Antibiotics (cefazolin sodium; Apothecon, Princeton, NJ) and analgesic drugs (buprenophine hydrochloride, 0.3 mg; Reckitt and Coleman, Kingston-upon-Hull, UK) were given postoperatively. During the first surgical procedure, the carotid arteries were placed in skin tubes in the neck so that they could be cannulated percutaneously to measure arterial blood pressure (13, 15). In the second surgery, all dogs were instrumented with flow probes (4- or 6-mm ultrasonic transit-time flow probes; Transonic Systems, Ithaca, NY) around the external iliac artery in each hindlimb to measure hindlimb blood flow. The cables were then tunneled under the skin to the back. The dogs were given 2 wk to recover from flow probe implantation. In the final surgery, a heparinized catheter (0.045 in. OD, 0.015 in. ID, 60 cm long; Data Science International, St. Paul, MN) was implanted chronically through a side branch into the femoral artery for drug infusion. The catheter was tunneled to the back of the dog. The catheter was flushed daily with saline and filled with a heparin lock (100 IU heparin/ml in 50% dextrose solution) to maintain patency. The dogs were given at least 2 days to recover from the final surgery before any experiments were performed.

All experiments were performed in a laboratory in which the temperature was maintained below 20°C. A 20-gauge Teflon catheter (Angiocath; Deseret, Sandy, UT) was inserted retrogradely into the lumen of the carotid artery and attached to a solid-state pressure transducer (Viggo-Spectramed, Oxnard, CA). The flow probes were connected to a transit-time flow meter (Transonic Systems, Ithaca, NY). The dogs ran on the treadmill at three different intensities: 3 miles/h (mph; 4.8 km/h), 0% grade; 6 mph (9.7 km/h) 0% grade; and 6 mph (9.7 km/h) 10% grade. Prazosin, a selective \( \alpha_1 \)-antagonist (Pfizer, Groton, CT), was dissolved in propylene glycol and diluted with sterile water to a concentration of 0.1 mg/ml. On separate days, the dogs received a bolus injection of 0.1 mg of prazosin into one femoral artery at rest, while running on the treadmill at 2 min of exercise at all intensities, and at 15 min of exercise at the two lowest intensities. Administration of prazosin at two time points allowed examination of time-dependent differences in sympathetic restraint of blood flow over a 15-min exercise bout, as reported previously by Petersen et al. (19). The ability of this dose of prazosin to block
1-adrenergic effects was tested in each dog in a separate session. While the dog ran at the 3 mph, 0% grade intensity, 25 µg of phenylephrine were infused into the femoral artery catheter before and after intra-arterial administration of prazosin. This test dose of phenylephrine was chosen because it produced substantial reductions in blood flow at rest and exercise.

Arterial blood pressure and right and left external iliac blood flow were written simultaneously on paper on a polygraph recorder (Grass, West Warwick, RI) and stored on both a videocassette data recorder (Vetter, Rebersburg, PA) and on a computer (Apple 8500 Power PC) using a MacLab system at 100 Hz (ADInstruments, Castle Hill, Australia). Data were analyzed off-line by using the MacLab software to calculate mean arterial pressure, heart rate (HR), iliac blood flow, and iliac vascular conductance (mean arterial pressure/blood flow). Vascular conductance was calculated rather than vascular resistance, because Lautt (11) has argued that conductance better reflects vascular tone when the experimental manipulation causes a change primarily in flow and not pressure. Control measurements were averaged over 30 s before prazosin infusion. After administration of 0.1 mg of prazosin, a subsequent infusion of phenylephrine produced no change in blood flow. In every dog, this dose of prazosin abolished the reduction in iliac blood flow produced by intra-arterial infusion of phenylephrine.

Table 1 presents baseline hemodynamics at the three workloads before drug infusion at 2 min into exercise. There were significant increases in HR ($P = 0.0003$), blood pressure ($P = 0.0053$), and blood flow ($P = 0.0001$) as exercise intensity increased. Intra-arterial infusion of the solvent vehicle did not affect any of these values. Furthermore, with the exception of blood flow in the experimental limb, all these variables remained

RESULTS

Figure 1 is an original record from an individual dog exercising on the treadmill at 3 mph. Infusion of 25 µg of phenylephrine into the femoral artery of the experimental limb reduced iliac blood flow from a mean of 218 to 101 ml/min. After administration of 0.1 mg of prazosin, a subsequent infusion of phenylephrine produced no change in blood flow. In every dog, this dose of prazosin abolished the reduction in iliac blood flow produced by intra-arterial infusion of phenylephrine.

![Fig. 1. Original record from dog exercising on the treadmill at 3 miles/h (mph). Intra-arterial infusion of $\alpha_1$-agonist phenylephrine (25 µg) into femoral artery of experimental limb reduced iliac blood flow and conductance. Intra-arterial administration of selective $\alpha_1$-antagonist prazosin (0.1 mg) abolished blood flow and conductance changes to subsequent infusion of phenylephrine. There were no changes in blood flow or conductance in control (contralateral) limb.](image-url)
unchanged after the intra-arterial bolus of prazosin (P > 0.05).

At rest, intra-arterial infusion of prazosin increased iliac blood flow from 79 ± 19 to 437 ± 32 ml/min (mean increase 605 ± 167%) and iliac conductance from 0.82 ± 0.2 to 4.56 ± 0.24 ml · min⁻¹ · mmHg⁻¹ (mean increase 628 ± 176%). Figure 2 shows an original record of an experiment in which prazosin was infused intra-arterially while the dog was running at 6 mph. In the experimental limb, there were immediate increases in blood flow and conductance that remained elevated above baseline for several minutes. There were no corresponding changes in HR, control limb blood flow, or systemic blood pressure. After prazosin infusion at 2 min of exercise, blood flow increased by 323 ± 34 to 795 ± 62 ml/min at 3 mph, by 269 ± 33 to 899 ± 84 ml/min at 6 mph, and by 173 ± 50 to 1,130 ± 85 ml/min at 6 mph and 10% grade. Figure 3 summarizes the absolute and percentage changes in iliac conductance resulting from intra-arterial prazosin infusion for the three different exercise intensities. There was a significant (P < 0.001) prazosin-induced increase in iliac conductance at each workload (76 ± 7% at 3 mph, 54 ± 11% at 6 mph, 22 ± 6% at 6 mph and 10% grade). Moreover, there was a significant drug × exercise-intensity interaction (P = 0.0001), such that there was an inverse relationship between the magnitude of sympathetic vasoconstriction and exercise intensity. The increase in iliac conductance was greatest at 3 mph and least at 6 mph, 10% grade (P < 0.01).

At 15 min of exercise, at both 3 and 6 mph, there was a significant (P = 0.0001) increase in conductance with intra-arterial prazosin. As shown in Fig. 4, the increase in iliac conductance produced by intra-arterial prazosin did not significantly differ between 2 and 15 min at either intensity (P > 0.05).

**DISCUSSION**

The observation of increases in blood flow after intra-arterial infusion of the α₁-antagonist prazosin demonstrates the existence of sympathetic vasoconstri-

**Table 1. Baseline hemodynamics during exercise before prazosin infusion**

<table>
<thead>
<tr>
<th>Exercise Condition</th>
<th>Heart Rate, beats/min</th>
<th>MAP, mmHg</th>
<th>Control</th>
<th>Experimental</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mph, 0% grade</td>
<td>142 ± 8</td>
<td>115 ± 5</td>
<td>459 ± 33</td>
<td>472 ± 41</td>
</tr>
<tr>
<td>6 mph, 0% grade</td>
<td>171 ± 17</td>
<td>122 ± 7</td>
<td>681 ± 92</td>
<td>630 ± 96</td>
</tr>
<tr>
<td>6 mph, 10% grade</td>
<td>213 ± 10</td>
<td>139 ± 5</td>
<td>982 ± 77</td>
<td>957 ± 99</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean arterial pressure; mph, miles/h.
tion in working muscles during dynamic exercise. In addition, the results show that the magnitude of sympathetic vasoconstriction is intensity dependent, being the greatest at the lowest intensity and decreasing as exercise intensity increases.

Several previous investigations have also provided evidence for sympathetic restraint of blood flow to active skeletal muscle (8, 14, 19, 25). In the study by Peterson et al. (19), muscle blood flow did not differ between intact rats and sympathectomized rats at 30 s and at 2 min into treadmill exercise; however, by 5 and 15 min, total hindlimb blood flow was significantly greater in the sympathectomized rats. In the present study, there was no difference in the magnitude of sympathetic vasoconstriction in dogs at 2 and 15 min of exercise. Joyner et al. (8) produced sympathetic blockade in human subjects with local anesthetic blockade of the stellate ganglion. After stellate block, there was a significant increase in ipsilateral forearm blood flow during rhythmic arm exercise. Studies by Vatner et al. (25) and Mittelstadt et al. (14) have demonstrated the potential for reflex modulation of skeletal muscle blood flow during exercise, presumably because of altered sympathetic outflow.

In contrast, results from other studies (4, 5, 10, 12) failed to provide evidence for the existence of sympathetic restraint of blood flow to working skeletal muscle. Longhurst et al. (12) and Laughlin and Armstrong (10) administered phentolamine (nonselective α-adrenergic antagonist) before exercise and made blood flow measurements with radioactive microspheres in exercising dogs and rats, respectively. Although there were no differences in skeletal muscle blood flow between conditions in either study, the results may have been confounded by higher HR and lower arterial pressures during exercise with phentolamine. Similar results were obtained in humans by Hartling and Trap-Jensen (5). They reported that phentolamine had no effect on forearm blood flow during forearm exercise. After administration of phentolamine, their subjects also manifested increases in HR and decreases in blood pressure. Perhaps the strongest evidence for the lack of sympathetic restraint of blood flow during exercise came from Donald et al. (4), who found no difference in hindlimb blood flow in surgically sympathectomized dogs that exercised on a treadmill at various workloads. In contrast to our experiments using acute sympathetic blockade, the experimental measurements of Donald and colleagues were made hours to days after the sympathectomy. We reconcile the results of these two studies by concluding that there is sympathetic restraint of blood flow during exercise under normal conditions but that other compensatory mechanisms restore blood flow to baseline levels after chronic abrogation of sympathetic tone.

In the present study, intra-arterial infusion of prazosin at rest also produced large increases in blood flow and conductance in the experimental limb. This finding demonstrates that there is substantial sympathetic...
restraint of blood flow to resting skeletal muscle and is consistent with the results of previous studies that have reported resting skeletal muscle blood flow after abrogation of sympathetic activity. Donald et al. (4) reported that the immediate response to section of the lumbar sympathetic nerves was a two- to threefold increase in iliac blood flow. Calculations made from the data of Laughlin and Armstrong (10) reveal that adrenergic blockade with phentolamine produced a 270% increase in hindlimb vascular conductance. The data from O’Leary et al. (16) show that ganglionic blockade produced ∼20% increase in terminal aortic conductance. In the studies by J oyner et al. (8), acute stellate blockade produced a threefold increase in forearm blood flow. The greater magnitude of the response reported in the present study compared with the prior studies is most likely a result of the unique experimental design employed in this study.

There were several advantages to our experimental approach compared with previous investigations: 1) acute selective α1-adrenergic blockade of one hindlimb, 2) continuous measurement of blood flow, and 3) use of a selective α2-antagonist. As shown in Fig. 1, intrararterial infusion of prazosin completely blocked the vasoconstriction induced by phenylephrine. Importantly, this blockade was produced at a low dose that prevented measurable systemic effects. In essence, this produced a functionally isolated hindlimb because the effect of prazosin was limited to the experimental limb, with no measurable changes in the contralateral hindlimb. Blood flow to the exercising hindlimb was measured continuously by using transit-time flow probes. Continuous measurement of blood flow facilitates detection of transient changes that may be missed with discrete measurements of blood flow with techniques such as radioactive microspheres, indicator dilution, or plethysmography. Finally, the use of a selective α2-antagonist, prazosin, provides a distinct advantage over use of the nonselective blocker phentolamine. Phentolamine blocks α2- as well as prejunctional α1-receptors that could increase norepinephrine release from the sympathetic nerve terminals. Furthermore, phentolamine has been shown to inhibit histamine-mediated vasodilation (21). Both of these effects could be confounding factors in previous investigations of skeletal muscle blood flow during exercise (5, 10, 12).

In this study, intra-arterial infusion of prazosin produced marked iliac vasodilation followed by a return of blood flow toward baseline levels. The transient nature of the observed increase in iliac blood flow is similar to what we have observed after acute section of the lumbar sympathetic trunk in anesthetized animals. In support of this, Donald et al. (4) reported that the immediate response to surgical sympathectomy was a two- to threefold increase in iliac blood flow, although 4 h later there was no difference in flow between the sympathectomized and control limbs. We reason that the return toward baseline blood flow in the present experiments does not indicate diminishing effectiveness of the blockade because subsequent infusion of phenylephrine had no effect and because a similar phenomenon occurs after surgical sympathectomy. We postulate that the transient response reflects activation of compensatory control mechanisms.

The hindlimb vasculature of the dog possesses β-adrenergic as well as α-adrenergic receptors. One might speculate that the vasodilation observed with prazosin in this study may be due to an unmasking of β-receptors after α-blockade. This prospect seems unlikely, considering that the largest increases in blood flow were seen at rest when circulating catecholamine concentrations should have been the lowest. Furthermore, from preliminary data (data now shown) in two dogs studied at the same exercise intensities, intra-arterial propranolol did not alter the hyperemic response seen with intra-arterial prazosin.

A thorough explanation for the mechanism for the inverse relationship between sympathetic vasoconstriction and exercise intensity is beyond the scope of this study. However, a decreased sensitivity to adrenergic agonists in skeletal muscle vasculature during exercise has been termed “functional sympatholysis” by Remensnyder et al. (20). Sympatholysis, manifested as diminished vasoconstriction during muscular activity in response to direct stimulation of the sympathetic nerves or administration of norepinephrine, has been demonstrated in a number of studies (1, 9, 20, 22, 24). These findings are consistent with the idea that muscle blood flow during exercise is ultimately determined by a competition between metabolic vasodilation and neurogenic vasoconstriction (2). Sympatholysis may persist even at rest after an acute bout of exercise. An exercise-induced decrease in vascular responsiveness to phenylephrine was shown by Howard and DiCarlo, both in vitro (7) and in vivo (6). However, it must be noted that this concept remains controversial. As pointed out by O’Leary et al. (17), recalculation of Kjellmer’s data (9) as vascular conductance rather than as vascular resistance eliminates the differences between resting and active skeletal muscle. Furthermore, O’Leary et al. (17) found no diminished baroreflex-mediated sympathetic vasoconstriction in dynamically exercising skeletal muscle in the dog, although their findings may be explained by the possibility that the reflex changes in sympathetic outflow were not uniform across workloads. The present results, showing an inverse relationship between sympathetic vasoconstriction and exercise intensity, are consonant with the concept of exercise-induced sympatholysis. However, another possible explanation of the inverse relationship between sympathetic vasoconstriction and exercise intensity may be related to the effective dose of the α-antagonist that would have been diluted by the higher blood flows at the higher exercise intensities.

The results from the present study show that acute blockade of α-adrenergic receptors in the vasculature of exercising skeletal muscles produces vasodilation. These data demonstrate that there is sympathetic vasoconstriction in active skeletal muscles even at high exercise intensities.
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