**α-Adrenergic vasoconstriction in active skeletal muscles during dynamic exercise**

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**Buckwalter, John B., and Philip S. Clifford.** α-Adrenergic vasoconstriction in active skeletal muscles during dynamic exercise. Am. J. Physiol. 277 (Heart Circ. Physiol. 46): H33–H39, 1999.—Sympathetic vasoconstriction in working muscles during dynamic exercise has been demonstrated by intra-arterial administration of α₁-adrenergic antagonists. The purpose of this study was to examine the existence of α₁- and α₂-adrenergic receptor-mediated vasoconstriction in active skeletal muscles during exercise. Six mongrel dogs were instrumented chronically with flow probes on the external iliac arteries of both hindlimbs, and a catheter was inserted in one femoral artery. All dogs ran on a motorized treadmill at three exercise intensities (3 miles/h, 6 miles/h, and 6 miles/h at 10% grade) on separate days. After 5 min of exercise, a selective α₁-(prazosin) or a selective α₂-adrenergic antagonist (rauwolscine) was infused as a bolus into the femoral arterial catheter (only one drug per day). The doses of the antagonists were adjusted to maintain the same effective concentration at each exercise intensity. At the mild, moderate, and heavy workloads prazosin infusion produced immediate increases in iliac conductance of 65 ± 9, 35 ± 6, and 18 ± 4% (means ± SE), respectively, and increases in blood flow of 290 ± 24, 216 ± 23, and 172 ± 18 ml/min, respectively. Rauwolscine infusion produced increases in conductance of 52 ± 5%, 36 ± 5%, and 26 ± 3%, respectively, and blood flow increases of 250 ± 34, 244 ± 39, and 259 ± 35 ml/min at the three workloads. Systemic blood pressure and blood flow in the contralateral iliac artery were unaffected by any of the antagonist infusions. These results demonstrate that there is a significant sympathetic vasoconstriction in exercising skeletal muscles even at heavy workloads and that the magnitude of vasoconstriction decreases as exercise intensity increases.

**Methods and Procedures**

All experimental procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the American Physiological Society's "Guiding Principles in the Care and Use of Animals." Mongrel dogs (n = 6, 21.3 ± 0.21 kg) were selected for their willingness to run on a motorized treadmill and were chronically instrumented using sterile surgical procedures. Anesthesia was...
induced with thiopental sodium (15–30 mg/kg; Genesia Pharmaceuticals, Irvine, CA) and maintained by mechanical ventilation with 1.5% halothane (Halocarbon Laboratories, River Edge, NJ) and 98.5% oxygen after intubation with a cuffed endotracheal tube. Antibiotic (cefazolin sodium, Apothecon, Princeton, NJ) and analgesic drugs (buprenorphine hydrochloride, 0.3 mg; Reckitt and Colman, Kingston-Upon-Hull, UK) were given postoperatively. During the initial surgical procedure, the carotid arteries were surgically exteriorized so that they could be cannulated percutaneously to measure arterial blood pressure (23, 24). In the second surgery, the dogs were instrumented with 4-mm ultrasonic transit time flow probes (Transonic Systems, Ithaca, NY) around the external iliac arteries to provide measurements of hindlimb blood flow. The cables were tunneled under the skin to the back, and the dogs were given 2 wk to recover. In the final surgery, a heparinized catheter for drug infusion (0.045-in. OD, 0.015-in. ID, 60-cm length, Data Science International, St. Paul, MN) was implanted through a skin incision into the femoral artery and the free end was tunneled to the back of the dog. To maintain patency, the catheter was flushed daily with saline and filled with a heparin lock (100 IU heparin/ml in 50% dextrose solution). The dogs were given at least 2 days to recover from the final surgery before any experiments were performed.

On each experimental day the dog was brought to the laboratory, which was maintained at a temperature below 20°C. A 20-gauge catheter (Insyte, Becton-Dickinson, Sandy, UT) was inserted retrogradely into the lumen of the carotid artery and attached to a solid-state pressure transducer (Ohmeda, Madison, WI). The dogs were placed on a motorized treadmill (Quinton Instruments, Seattle, WA), and the flow probes were connected to a transit time flowmeter (Transonic Systems). On separate days, the dogs ran at three different exercise intensities: 3 miles/h (4.8 km/h) 0% grade, 6 miles/h (9.7 km/h) 0% grade, or 6 miles/h (9.7 km/h) 10% grade. Prazosin, a selective α1-antagonist (Pfizer, Groton, CT), was dissolved in propylene glycol and diluted with sterile water to a concentration of 200 µg/ml. Rauwolscine, a selective α2-antagonist (RBI, Natick, MA), was dissolved in sterile water to a concentration of 2 mg/ml. Both of these antagonists have been previously shown to be effective at producing selective α-adrenergic blockade in skeletal muscle (1, 9). The dogs ran on the treadmill at 3 miles/h. At 5 min of exercise, a bolus of antagonist (50 µg prazosin or 1 mg rauwolscine) was infused into one femoral artery. Antagonist infusions were given at the same time point at the two higher exercise intensities. The dose of the antagonist was proportionally adjusted to account for the exercise intensity-induced increases in iliac blood flow (drug dose = 3 miles per hour x exercise blood flow/3 miles per hour x blood flow). The doses of the selective α-adrenergic receptor antagonists used in this study were chosen because of their ability to abolish the substantial vasoconstriction induced by 10 µg of the α2-selective agonist phenylephrine and 10 µg of the α2-selective agonist clonidine, respectively. In each experiment, the selective α-adrenergic receptor antagonist completely abolished the effect of the appropriate agonist. All experiments were performed in duplicate, and the data were averaged for each dog. Only one bout of exercise and one receptor antagonist were examined per day (36 separate experiments on 36 separate days). Intraarterial infusions of the solvent vehicle have previously been shown not to affect iliac blood flow (2, 3).

Arterial blood pressure and right and left external iliac blood flow were written simultaneously to paper on a polygraph recorder (Grass, Quincy, MA) and stored on both a video cassette data recorder (Vetter, Rebersburg, PA) and computer (Apple 8500 Power PC) using a MacLab system at 100 Hz (ADInstruments, Castle Hill, Australia). Data were analyzed off-line using the MacLab software to calculate mean arterial pressure, heart rate, iliac blood flow, and iliac vascular conductance (blood flow/mean arterial pressure). Control measurements were averaged over 30 s before the antagonist infusion. After the antagonist infusion, all variables were averaged over 1-s intervals, and the highest 1-s average was chosen as the peak response. Statistical analyses of heart rate, mean arterial blood pressure, blood flow, and conductance were performed with a two-way (drug x exercise intensity) repeated-measures analysis of variance. The percent changes from baseline in conductance after the infusion of the antagonists were analyzed with a one-way repeated-measures analysis of variance. Where significant F ratios were found, a Tukey’s post hoc test was performed. All data are expressed as means ± SE.

RESULTS

Table 1 presents hemodynamic values at the three workloads before and after intra-arterial infusion of rauwolscine. There were significant increases in heart rate (P < 0.001) and blood flow (P < 0.001) as exercise intensity increased. With the exception of blood flow and conductance in the experimental limb, all of these variables remained unchanged following the intra-arterial bolus of rauwolscine (P > 0.05). Figure 3 is an original record from an individual dog exercising on the treadmill at 3 miles/h. Intra-arterial infusion of rauwolscine produced an immediate increase in blood flow in the experimental limb, with no change in blood flow in the control limb. In every dog, intra-arterial administration of rauwolscine abolished the reduction in iliac

### Table 1. Hemodynamic values before and after rauwolscine infusion

<table>
<thead>
<tr>
<th></th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>Control Limb Blood Flow, ml/min</th>
<th>Experimental Limb Blood Flow, ml/min</th>
<th>Control Limb Conductance, ml·min⁻¹·mmHg⁻¹</th>
<th>Experimental Limb Conductance, ml·min⁻¹·mmHg⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-rauwolscine</strong></td>
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</tr>
<tr>
<td>3 miles/h</td>
<td>106 ± 6</td>
<td>144 ± 13</td>
<td>478 ± 50</td>
<td>468 ± 52</td>
<td>4.57 ± 0.58</td>
<td>4.44 ± 0.49</td>
</tr>
<tr>
<td>6 miles/h</td>
<td>112 ± 6</td>
<td>172 ± 10</td>
<td>641 ± 39</td>
<td>634 ± 45</td>
<td>5.81 ± 0.59</td>
<td>5.67 ± 0.33</td>
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<tr>
<td>6 miles/h 10%</td>
<td>118 ± 3</td>
<td>215 ± 7†</td>
<td>1,026 ± 72†</td>
<td>976 ± 39†</td>
<td>8.74 ± 0.78†</td>
<td>8.28 ± 0.42†</td>
</tr>
<tr>
<td><strong>Post-rauwolscine</strong></td>
<td></td>
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</tr>
<tr>
<td>3 miles/h</td>
<td>107 ± 6</td>
<td>146 ± 15</td>
<td>475 ± 56</td>
<td>719 ± 83</td>
<td>4.49 ± 0.61</td>
<td>6.79 ± 0.88†</td>
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<tr>
<td>6 miles/h</td>
<td>114 ± 6</td>
<td>177 ± 11</td>
<td>647 ± 39</td>
<td>879 ± 77</td>
<td>5.81 ± 0.59</td>
<td>7.77 ± 0.62†</td>
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<tr>
<td>6 miles/h 10%</td>
<td>119 ± 5</td>
<td>216 ± 7</td>
<td>1,059 ± 78</td>
<td>1,236 ± 50</td>
<td>9.02 ± 0.96</td>
<td>10.43 ± 0.93†</td>
</tr>
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</table>

Values are means ± SE. MAP, mean arterial pressure; HR, heart rate; 10%, 10% grade. *Significantly different from 3 miles/h (P < 0.01); † significantly different from 6 miles/h (P < 0.01); ‡ significantly different after rauwolscine infusion (P < 0.01).
blood flow produced by intra-arterial infusion of 10 µg of clonidine.

Intra-arterial infusion of rauwolscine during exercise produced substantial increases in blood flow at all exercise intensities (P < 0.001). However, the absence of a significant drug times exercise intensity interaction (P = 0.62) indicates that there were no significant differences in the absolute changes in iliac blood flow or conductance among the three different exercise intensities. In contrast, there was a significant effect of exercise intensity on the percent changes in iliac blood flow (P < 0.001) and conductance (P < 0.001) resulting from intra-arterial infusions of rauwolscine. The percent increase in iliac conductance was greatest at 3 miles/h and least at 6 miles/h, 10% grade (Fig. 2).

Table 2 presents hemodynamic values at the three workloads before and after intra-arterial infusion of prazosin. There were significant increases in heart rate (P < 0.001), blood pressure (P < 0.03), and iliac blood flow (P < 0.001) with increases in exercise intensity. Furthermore, with the exception of blood flow and conductance in the experimental limb, all these variables remained unchanged following the intra-arterial bolus of prazosin (P > 0.05). Intra-arterial infusions of prazosin during exercise produced marked increases in blood flow and conductance at all exercise intensities (P < 0.001). There was a significant drug times exercise intensity interaction (P < 0.01), such that there was an inverse relationship between the absolute change in blood flow or conductance and exercise intensity (P < 0.001). A similar relationship was revealed for the percent changes in iliac blood flow and conductance after intra-arterial prazosin infusion (P < 0.001). The increase in iliac conductance was greatest at 3 miles/h and least at 6 miles/h, 10% grade (Fig. 2).

**DISCUSSION**

Intra-arterial infusion of selective α-adrenergic antagonists was employed in conscious, exercising animals to acutely interrupt the vasoconstrictor effects of exercise-induced sympathoexcitation. The major new finding from these experiments is the demonstration of tonic α2-adrenergic receptor-mediated vasoconstriction in working skeletal muscle during dynamic exercise, even during intense exercise. Second, because the effects of α1- and α2-adrenergic receptor blockade on vessel diameter are reflected by the percent change in conductance (see below), we conclude that the magnitude of tonic α-adrenergic receptor-mediated vasoconstriction was inversely related to exercise intensity. In other words, there was less sympathetic vasoconstriction in active muscle as exercise intensity increased. However, the effect of this tonic vasoconstriction on the restraint of blood flow was different for α1- and α2-adrenergic receptors. Exercise intensity did not appear
Systemic administration of the nonselective α-adrenergic blocker phentolamine failed to alter blood flow to the working skeletal muscle (12, 17, 19). In contrast, acute interruption of sympathetic vasoconstriction (14, 29, 38) revealed that there was sympathetic restraint of blood flow to exercising skeletal muscle. Two recent studies (2, 28) that employed intra-arterial infusion of selective α1-adrenergic antagonists to acutely interrupt sympathetic vasoconstriction provided clear evidence of α1-receptor-mediated vasoconstriction in working skeletal muscle. The findings of the present study extend the previous results by demonstrating that there is tonic α2-receptor-mediated vasoconstriction in active skeletal muscle in the conscious dog.

α2-Adrenergic receptors are found prejunctionally in proximity to the synapse as well as postjunctionally on vascular smooth muscle. The prejunctional α2-receptor is thought to act in an autoregulatory manner. Stimulation of prejunctional α2-receptors by norepinephrine released into the synapse inhibits further release of norepinephrine. To our knowledge there is no pharmacological agent that selectively binds only prejunctional or postjunctional α2-adrenergic receptors. In the present study, rauwolscine infusion caused an immediate vasodilation. We interpret this vasodilation to mean that the main effect of the drug was to antagonize postjunctional α2-receptors mediating constriction. If the main effect had been on the prejunctional α2-adrenergic receptors, there would have been greater release of norepinephrine from the synapse and a vasoconstrictor effect. It must be recognized that prejunctional α2-receptors were probably also antagonized by the rauwolscine. This could have increased norepinephrine release and α1-receptor vasoconstriction such that the magnitude of α2-receptor-mediated vasoconstriction was underestimated.

Postsynaptic α2-adrenergic receptors contribute to vascular tone in canine skeletal muscles (11, 16). In rats, Faber (9) demonstrated that both α1- and α2-adrenergic receptors are present on large arterioles, but only α2-receptors exist on the terminal arterioles. α1-Adrenergic receptors appear to exert the predominant control over the diameter of the large arterioles, whereas α2-receptors control the diameter of the terminal arterioles (26). The present study is the first to show tonic α2-adrenergic receptor-mediated vasoconstriction and to affect the magnitude of blood flow restrained by α2-adrenergic receptors, but there was an inverse relationship between tonic α1-adrenergic restraint of blood flow and exercise intensity.

A number of previous studies (7, 12, 17, 19) did not demonstrate the existence of sympathetic restraint of blood flow to exercising skeletal muscle. Systemic administration of the nonselective α-adrenergic blocker phentolamine failed to alter blood flow to the working skeletal muscle (12, 17, 19). In contrast, acute interruption of sympathetic vasoconstriction (14, 29, 38) revealed that there was sympathetic restraint of blood flow to exercising skeletal muscle. Two recent studies (2, 28) that employed intra-arterial infusion of selective α1-adrenergic antagonists to acutely interrupt sympathetic vasoconstriction provided clear evidence of α1-receptor-mediated vasoconstriction in working skeletal muscle. The findings of the present study extend the previous results by demonstrating that there is tonic α2-receptor-mediated vasoconstriction in active skeletal muscle in the conscious dog.

Fig. 2. Relationship between percent change in iliac conductance and exercise intensity after intra-arterial infusion of either rauwolscine or prazosin at 5 min of exercise. There was an inverse relationship between percent changes in iliac conductance and exercise intensity for both prazosin and rauwolscine. Data are expressed as means ± SE; 10%, 10% grade.

Table 2. Hemodynamic values before and after prazosin infusion

<table>
<thead>
<tr>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>Control Limb Blood Flow, ml/min</th>
<th>Experimental Limb Blood Flow, ml/min</th>
<th>Control Limb Conductance, ml·min⁻¹·mmHg⁻¹</th>
<th>Experimental Limb Conductance, ml·min⁻¹·mmHg⁻¹</th>
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<tr>
<td>Pre-prazosin</td>
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</tr>
<tr>
<td>3 miles/h</td>
<td>109 ± 4</td>
<td>145 ± 8</td>
<td>485 ± 56</td>
<td>471 ± 42</td>
<td>4.45 ± 0.54</td>
</tr>
<tr>
<td>6 miles/h</td>
<td>107 ± 6</td>
<td>170 ± 8*</td>
<td>631 ± 56*</td>
<td>606 ± 43*</td>
<td>5.94 ± 0.56*</td>
</tr>
<tr>
<td>6 miles/h 10%</td>
<td>116 ± 4†</td>
<td>216 ± 6*†</td>
<td>1,028 ± 77*†</td>
<td>941 ± 49*†</td>
<td>8.92 ± 0.72†</td>
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<td>Post-prazosin</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3 miles/h</td>
<td>108 ± 4</td>
<td>141 ± 10</td>
<td>491 ± 46</td>
<td>761 ± 60†</td>
<td>4.57 ± 0.46†</td>
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<tr>
<td>6 miles/h</td>
<td>108 ± 6</td>
<td>169 ± 8</td>
<td>628 ± 52</td>
<td>823 ± 54†</td>
<td>5.89 ± 0.55†</td>
</tr>
<tr>
<td>6 miles/h 10%</td>
<td>116 ± 4</td>
<td>219 ± 7</td>
<td>1,025 ± 84</td>
<td>1,114 ± 32†</td>
<td>8.82 ± 0.76†</td>
</tr>
</tbody>
</table>

Values are means ± SE. *Significantly different from 3 miles/h (P < 0.01); †significantly different from 6 miles/h (P < 0.01); ‡significantly different after prazosin infusion (P < 0.01).
striction in active skeletal muscle during voluntary dynamic exercise. The design of these experiments in conscious animals precluded determination of the relative effects of adrenergic blockade on larger arterioles versus terminal arterioles. However, it is likely that intra-arterial infusion of α-adrenergic antagonists in the present study interrupted ongoing α-adrenergic receptor-mediated vasoconstriction in the conduit arteries as well as the microcirculation.

Appropriate expression of data is essential for accurate interpretation in experiments designed to examine vasomotor function. Although not consistently used, it is recognized that vascular conductance, because of its linear relationship with flow, is a more appropriate expression of vasomotor function than of vascular resistance (18, 27). It has also been noted (33) that, when expressing changes in vascular tone from baseline, the percent change is more appropriate than the absolute change. Indeed, the percent change in conductance consistently reflects a calculable percent change in the radius of the vessel. If the desire is to compare the degree of vasoconstriction or vasodilation in a vascular bed, which by definition indicates a change in the vessel radius, the percent change in conductance more accurately reflects this change. These considerations are particularly important with comparisons of vasomotor tone between different exercise intensities where baseline blood flows are substantially different.

Absolute changes in conductance would vary considerably when identical changes in vessel radius are imposed on differing baseline blood flows, whereas a given percent reduction in conductance reflects predictable percent reduction in the radius of the vessel despite differing baseline blood flows.

In the present study, whether expressed as a percent change or an absolute change, there was an inverse relationship between the change in iliac conductance with intra-arterial prazosin and exercise intensity. However, examining the absolute change in conductance with intra-arterial rauwolscine would lead one to conclude inappropriately that there is the same degree of tonic vasoconstriction at each workload. Although O’Leary et al. (28) reported a linear relationship between α₁-mediated vasoconstriction (absolute change in conductance) and exercise intensity, when these data are replotted as a percent change in conductance, an inverse relationship between vasoconstriction and exercise intensity is revealed. By examining the percent change in iliac conductance in the present study, we conclude that intra-arterial infusion of α₁-adrenergic antagonists into the vasculature of skeletal muscle produced less inhibition of vasoconstriction as exercise intensity increased.

Direct recordings from sympathetic nerves have shown that increases in exercise intensity produce increases in sympathetic outflow to visceral organs (25) and skeletal muscle (6). We have previously reported (2), that despite this increase in sympathetic outflow, there is an inverse relationship between the magnitude of α₁-adrenergic receptor-mediated vasoconstriction in active skeletal muscle and exercise intensity. However, in that study a fixed dose (100 µg) of prazosin was used and may have been diluted by the higher blood flows at the higher exercise intensities. That limitation was overcome in the present study by the dose adjustment of the α₁-adrenergic receptor antagonists in proportion to the exercise-induced increases in blood flow. Greater doses of prazosin were administered at higher exercise intensities but did not alter the inverse relationship between α₁-adrenergic receptor-mediated vasoconstriction and exercise intensity. A similar relationship was seen between α₂-adrenergic receptor-mediated vasoconstriction and exercise intensity. Thus we conclude that the magnitude of tonic α₁-adrenergic receptor-mediated vasoconstriction is inversely related to exercise intensity.

A decreased sensitivity to sympathetic stimulation or adrenergic agonists in the skeletal muscle vasculature during exercise was first described by Rein (30) and termed “functional sympatholysis” by Remensnyder et al. (31). Although the existence of sympatholysis has been controversial, it is clear that there is not total abrogation of sympathetic control in active skeletal muscle (2, 28). Muscle perfusion is ultimately a competition between metabolic vasodilation and sympathetic vasoconstriction. The results from the present study agree with other studies that show sympathetic vasoconstriction can be attenuated in active skeletal muscle by heavy exercise (2, 15, 35). One proposed mechanism for sympatholysis involves metabolic inhibition of α₂-receptors. There appears to be a differential sensitivity of α₁- and α₂-adrenergic receptors to metabolic inhibition. α₂-Adrenergic receptor-mediated vasoconstriction in skeletal muscle appears to be particularly sensitive to modest reductions in pH (20, 22, 36). In addition, hypoxia (20, 36), ischemia (21), and muscle contractions (1, 37) have been shown to inhibit α₂-adrenergic receptor-mediated vasoconstriction in the arterial vasculature of skeletal muscle. On the other hand, α₁-adrenergic receptor-mediated vasoconstriction appears to be unaffected by changes in pH (20, 22, 36), hypoxia (20, 36), or ischemia (21). The effect of electrically stimulated muscle contractions on α₁-adrenergic receptor-mediated vasoconstriction is less consistent (1, 37). Anderson and Faber (1) showed an attenuation of α₁-adrenergic receptor-mediated vasoconstriction during intense muscle contractions, but Thomas et al. (37) reported no attenuation of α₁-adrenergic receptor-mediated vasoconstriction during muscle contractions. The present results showing inverse relationships between α₁- and α₂-adrenergic receptor-mediated vasoconstriction and exercise intensity are consistent with the concept of exercise-induced sympatholysis. However, the demonstration of an inverse relationship between vasoconstriction and exercise intensity for both α₁- and α₂-adrenergic receptors does not reflect a differential sensitivity of these two subtypes of receptors.

Although this discussion has focused on the relative degree of vasoconstriction or vasodilation in the skeletal muscle vasculature, it is recognized that the abso-
lute changes in blood flow have physiological relevance in regard to blood pressure regulation. As exercise intensity increases, sympathetic vasoconstriction in active skeletal muscle becomes progressively more important for the regulation of systemic blood pressure (32). The relationship between exercise intensity and absolute changes in blood flow differed between prazosin and rauwolscine, with α1-restraint of blood flow decreasing across workloads and α2-restraint of blood flow constant across workloads. One might assume that similar absolute changes in blood flow with rauwolscine infusion indicate similar contributions to systemic blood pressure regulation at each exercise intensity. However, the effect of a given change in blood flow on blood pressure regulation becomes smaller as total vascular conductance rises with increasing exercise intensity. In other words, the change in mean arterial pressure is inversely proportional to the total vascular conductance. Because cardiac output and total vascular conductance are inversely related to exercise intensity, the change in mean arterial pressure is less with increasing exercise intensity. In conclusion, the results from this study show that there is considerable α1- and α2-adrenergic receptor-mediated vasoconstriction in active skeletal muscles even at heavy exercise intensities. In addition, the magnitude of tonic α-adrenergic receptor-mediated vasoconstriction in exercising skeletal muscles is inversely related to exercise intensity.

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