Exercise attenuates \( \alpha \)-adrenergic-receptor responsiveness in skeletal muscle vasculature

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Buckwalter, John B., Jay S. Naik, Zoran Valic, and Philip S. Clifford. Exercise attenuates \( \alpha \)-adrenergic-receptor responsiveness in skeletal muscle vasculature. J Appl Physiol 90: 172–178, 2001.—Attenuation of sympathetic vasoconstriction (sympatholysis) in working muscles during dynamic exercise is controversial. A potential mechanism is a reduction in \( \alpha \)-adrenergic-receptor responsiveness. The purpose of this study was to examine \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic-receptor-mediated vasoconstriction in resting and exercising skeletal muscle using intra-arterial infusions of selective agonists. Thirteen mongrel dogs were instrumented chronically with flow probes on the external iliac arteries of both hindlimbs and a catheter in one femoral artery. The selective \( \alpha_1 \)-adrenergic agonist (phenylephrine) or the selective \( \alpha_2 \)-adrenergic agonist (clonidine) was infused as a bolus into the femoral artery catheter at rest and during mild and heavy exercise. Intra-arterial infusions of phenylephrine elicited reductions in vascular conductance of 76 ± 4, 71 ± 5, and 31 ± 2\% at rest, 3 miles/h, and 6 miles/h and 10\% grade, respectively. Intra-arterial clonidine reduced vascular conductance by 81 ± 5, 49 ± 4, and 14 ± 2\%, respectively. The response to intra-arterial infusion of clonidine was unaffected by surgical sympathetic denervation. Agonist infusion did not affect either systemic blood pressure, heart rate, or blood flow in the contralateral iliac artery. \( \alpha_1 \)-Adrenergic-receptor responsiveness was attenuated during heavy exercise. In contrast, \( \alpha_2 \)-adrenergic-receptor responsiveness was attenuated even at a mild exercise intensity. These results suggest that the mechanism of exercise sympatholysis may involve reductions in postsynaptic \( \alpha \)-adrenergic-receptor responsiveness.

blood flow; sympatholysis; autonomic nervous system; dogs; vasoconstriction

AT THE ONSET OF EXERCISE, THERE IS A SUBSTANTIAL INCREASE IN OXYGEN DEMAND IN EXERCISING SKELETAL MUSCLE. THIS REQUIREMENT IS MET BY THE REDISTRIBUTION OF CARDIAC OUTPUT AWAY FROM INACTIVE TISSUES AND BY LARGE INCREASES IN BLOOD FLOW TO THE WORKING MUSCLES. THE ABILITY OF THE SYMPATHETIC NERVOUS SYSTEM TO RESTRAIN BLOOD FLOW IN ACTIVE SKELETAL MUSCLE DURING EXERCISE HAS BEEN CONTROVERSIAL. A NUMBER OF STUDIES HAVE REPORTED NO SYMPATHETIC RESTRAINT OF BLOOD FLOW IN WORKING SKELETAL MUSCLE (7, 11, 16, 18). HOWEVER, THE PREPONDERANCE OF THE EVIDENCE SHOWS THERE IS INDEED SYMPATHETIC RESTRAINT OF SKELETAL MUSCLE HYPEREMIA DURING EXERCISE (3, 12, 26, 27, 33). ALTHOUGH IT APPEARS CLEAR THAT THERE IS SYMPATHETICALLY MEDIATED VASOCONSTRICTION IN ACTIVE SKELETAL MUSCLE, WHETHER THIS VASOCONSTRICTION IS ATTENUATED FROM REST IS LESS CERTAIN. INDEED, IT HAS BEEN ARGUED THAT AS EXERCISE INTENSITY INCREASES THERE IS AN INCREASE IN SYMPATHETIC VASOCONSTRICTION IN ACTIVE SKELETAL MUSCLE (26). AN ATTENUATION OF VASOCORSTRICTION IN THE ARTERIAL VASCULARITY OF SKELETAL MUSCLE DURING MUSCLE CONTRACTION HAS BEEN REPORTED TO NUMBER OF INVESTIGATORS (5, 13, 14, 28, 29, 32). THIS DIMINISHED VASCULAR RESPONSIVENESS TO SYMPATHETIC STIMULATION DURING MUSCULAR CONTRACTION WAS TERMED “SYMPATHOLYSIS” BY REMENSNYDER ET AL. (28).

RECENTLY, IT HAS BEEN PROPOSED THAT THE \( \alpha_2 \)-ADRENERGIC RECEPTOR HAS A PROMINENT ROLE IN EXERCISE SYMPATHOLYSIS (1, 31). ALTHOUGH \( \alpha_2 \)-ADRENERGIC RECEPTORS WERE ORIGINALLY BELIEVED TO BE LOCATED ONLY ON THE PRESYNAPTIC NERVE TERMINAL, SUBSEQUENT STUDIES DEMONSTRATED THE EXISTENCE OF POSTSYNAPTIC \( \alpha_2 \)-RECEPTORS IN VASCULAR SMOOTH MUSCLE (8). POSTSYNAPTIC \( \alpha_2 \)-ADRENERGIC RECEPTORS CONTRIBUTE TO THE NEURALLY MEDIATED TONE IN THE SKELETAL MUSCLE VASCULARITY OF THE ANESTHETIZED DOG (10, 15). FURTHERMORE, OUR GROUP HAS RECENTLY DEMONSTRATED THE EXISTENCE OF TONIC \( \alpha_2 \)-ADRENERGIC-RECEPTOR MEDIATED VASOCONSTRICTION IN ACTIVE SKELETAL MUSCLE OF CONSCIOUS DYNAMICALLY EXERCISING DOGS (2). \( \alpha_2 \)-ADRENERGIC RECEPTORS APPEAR TO BE PARTICULARLY SENSITIVE TO MODEST REDUCTIONS IN pH (19, 21, 30). IN ADDITION, HYPOXIA (19, 30), ISCHEMIA (20), AND ELECTROLYTICALLY STIMULATED MUSCLE CONTRACTIONS (1, 31) HAVE BEEN SHOWN TO INHIBIT \( \alpha_2 \)-ADRENERGIC-RECEPTOR MEDIATED VASOCONSTRICTION IN THE ARTERIAL VASCULARITY OF SKELETAL MUSCLE. ON THE OTHER HAND, \( \alpha_1 \)-ADRENERGIC-RECEPTOR-MEDIATED VASOCONSTRICTION APPEARS TO BE UNAFFECTED BY CHANGES IN pH (19, 21, 30), HYPOXIA (19, 30), OR ISCHEMIA (20).

The purpose of this study was to examine exercise-induced alterations in \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic-receptor responsiveness in the vasculature of skeletal muscle. We used an experimental approach in conscious dogs that allowed examination of \( \alpha \)-adrenergic-receptor responsiveness in the vasculature of one hindlimb at rest and during exercise while not affecting systemic hemo-
dynamics. This experimental design employs intra-arterial infusion of small doses of vasoactive drugs in the vasculature of skeletal muscle and has been previously used to examine $\alpha_1$-adrenergic-receptor responsiveness at rest and during mild and moderate exercise (4). We hypothesized that $\alpha_2$- but not $\alpha_1$-adrenergic-receptor responsiveness would be attenuated from rest to exercise in an exercise intensity-dependent manner.

**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*. Six mongrel dogs (20–23 kg) were selected for their willingness to run on a motorized treadmill. The animals were chronically instrumented in a series of sterile surgical procedures. 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 (22, 23). During the second surgery, all dogs were instrumented with flow probes (4-mm ultrasonic transit-time flow probes, Transonic Systems, Ithaca, NY) around the external iliac artery to each hindlimb to measure skeletal muscle blood flow. The cables were then tunneled under the skin to the back. In the final surgery, a heparinized catheter (0.045-in. OD, 0.015-in. ID, 60-cm length, Data Science International, St. Paul, MN) for drug infusion was implanted chronically through a side branch into the femoral artery and tunneled to the back of the dog. For all surgical procedures, anesthesia was induced with thiopental sodium (15–30 mg/kg; Genisia Pharmaceuticals, Irvine CA). After intubation 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 (buprenorphine hydrochloride, 0.3 mg; Reckitt and Coleman, Kingston-upon-Hull, UK) were given postoperatively. To maintain patency, the femoral catheter was flushed daily with saline and filled with a heparin solution (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.

All experiments were performed in a laboratory in which the temperature was maintained below 20°C. On the day of the experiment, the dog was brought to the laboratory, a 20-gauge Teflon catheter (Inyte, Becton Dickinson, Deseret, Sandy, UT) was inserted retrogradely into the lumen of the carotid artery and attached to a solid-state pressure transducer (Ohmeda, Madison, WI), and the flow probes were connected to a transit-time flowmeter (Transonic Systems, Ithaca, NY). The dogs sat quietly in a restrictive sling, and into one hindlimb an intra-arterial bolus of either 5 $\mu$g of phenylephrine, a selective $\alpha_1$-agonist (American Regent Laboratories, Shirley, NY), or 5 $\mu$g of clonidine, a selective $\alpha_2$-agonist (RBI, Natick, MA) was given. These agonists were chosen for their ability to be dissolved in aqueous solution and infused in a conscious, chronically instrumented dog without detrimental effects. There were four infusions of the agonist at rest separated by at least 5 min, which was sufficient time for blood flow to return to baseline levels and avoid any tachyphylaxis to the drug. These data were averaged for determination of $\alpha$-adrenergic-receptor responsiveness at rest. The dog was then moved to the treadmill for examination of $\alpha$-adrenergic-receptor responsiveness during exercise. For this study, the dogs ran on the treadmill at two different intensities: a mild exercise intensity of 3 miles/h (4.8 km/h) and 0% grade and a heavy exercise intensity of 6 miles/h (9.7 km/h) and 10% grade. The dog performed three bouts of exercise at either the mild or heavy exercise intensity separated by 10 min of rest. After 1 h of rest, the experiment was completed at the other exercise intensity in the same manner (the order of exercise intensity was counterbalanced). At 5 min of exercise, the selective agonist was infused. Shortly after blood flow returned to baseline (~1 min), the bout of exercise was stopped. Only one agonist was infused per day. The data from the three bouts of exercise were averaged for determination of $\alpha$-adrenergic-receptor responsiveness. We reasoned that because hindlimb blood flow increases in an exercise intensity-dependent manner, administration of an identical amount of agonist at rest and exercise would result in a lower effective concentration of the drug during exercise. Therefore, as in a previous investigation (4), the dose of the agonist administered during exercise was increased from rest. Five micrograms of phenylephrine or clonidine were infused into one hindlimb at rest, and the average effective concentration of the drug ($\mu$g of drug/ml of blood flow) was calculated for each individual dog. The same effective concentration was then administered during exercise by increasing the dose in proportion to the increase in blood flow (exercise drug dose = resting drug dose x exercise blood flow/resting blood flow). To calculate drug dose during exercise, steady-state blood flow measurements were averaged over 30 s starting 90 s before the point of drug infusion.

Intra-arterial infusion of the selective $\alpha_2$-agonist clonidine may stimulate $\alpha_2$-adrenergic receptors on the prejunctional synapse as well as postjunctionally on vascular smooth muscle. The prejunctional $\alpha_2$-Receptor is thought to act in an autoregulatory manner and inhibit the release of norepinephrine when stimulated. To our knowledge, there is no pharmacological agonist that selectively binds only postjunctional $\alpha_2$-adrenergic receptors. Because interpretation of reductions in vascular conductance produced by intra-arterial infusions of clonidine may be confounded by interruption of tonic norepinephrine release produced by stimulation of prejunctional $\alpha_2$-receptors, a separate set of seven dogs (20–23 kg) were studied after unilateral hindlimb sympathectomy (which would abolish tonic release of norepinephrine). Chronic sympathectomy was achieved by dissecting and excising the lumbar sympathetic chain from L4 to L6. The animals were allowed to recover for 30 days after the sympathectomy. After recovery, efficacy of the surgical sympathectomy was confirmed by examining the vasomotor response to 30 s of bilateral carotid arterial occlusion. After confirmation of sympathetic denervation, clonidine was infused intra-arterially into the sympathectomized hindlimb at rest and during exercise as described above.

During all experiments, arterial blood pressure and right and left external iliac blood flow were written simultaneously to paper on a polygraph recorder (Grass, West Warwick, RI) 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). Vascular conductance was calculated rather than vascular resistance because Lautt (17) 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 agonist infusion. After the agonist infusion, all variables were averaged over 1-s intervals (100 consecutive data
Fig. 1. Two original records from an individual dog exercising on the treadmill at 6 miles/h and 10% grade. Arrows indicate intra-arterial infusion of a selective α₁-agonist, phenylephrine, or a selective α₂-agonist, clonidine, into the femoral artery of the experimental limb. Both infusions produced immediate reductions in iliac blood flow. Note that there were no changes in blood pressure or blood flow in the control (contralateral) limb in either tracing. Interestingly, in this particular dog, the agonists produced similar reductions (phenylephrine 78%, clonidine 76%) in conductance at rest (data not shown). However, the magnitude of vasoconstriction produced during intense exercise was quite different, indicating a greater attenuation of α₂-adrenergic-receptor responsiveness than α₁-adrenergic receptor responsiveness.

Table 1. Baseline hemodynamic values before phenylephrine infusion

<table>
<thead>
<tr>
<th>Control Limb</th>
<th>Experimental Limb</th>
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</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>88 ± 7</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>99 ± 8</td>
</tr>
<tr>
<td>Blood flow, ml/min</td>
<td>139 ± 32</td>
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<tr>
<td>Conductance, ml/min−1·mmHg−1</td>
<td>1.32 ± 0.29</td>
</tr>
<tr>
<td>Blood flow, ml/min</td>
<td>133 ± 34</td>
</tr>
<tr>
<td>Conductance, ml/min−1·mmHg−1</td>
<td>1.26 ± 0.28</td>
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Values are means ± SE. HR, heart rate; MAP, mean arterial pressure. *Significantly different from rest, P < 0.01. †Significantly different from 3 miles/h, P < 0.01.
of clonidine produced significant (P = 0.0005) reductions in experimental limb blood flow of 102 ± 9, 231 ± 23, and 150 ± 13 ml/min at rest, 3 miles/h, and 6 miles/h and 10% grade, respectively. None of these infusions caused a change in blood flow in the contralateral limb, mean arterial pressure, or heart rate. As seen in Fig. 3, mild exercise significantly (P < 0.01) attenuated the percent change in iliac conductance elicited by clonidine compared with rest. The percent change in iliac conductance was further attenuated (P < 0.01) by heavy exercise such that there was only a small response to the infusion of clonidine. Proportionally adjusted doses, used to maintain the same effective concentration of clonidine, averaged 22 ± 5 and 52 ± 13 µg at the two exercise intensities. These results do not appear to be confounded by stimulation of prejunctional α2-receptors since intra-arterial infusions of clonidine into a sympathectomized hindlimb produced similar results (Fig. 4). Efficacy of the lumbar sympathectomy was confirmed by bilateral carotid occlusion that produced a baroreflex-mediated decrease in conductance in the control limb but not in the sympathectomized limb (Fig. 5).

**DISCUSSION**

There are two major new findings in this study. First, α2-adrenergic-receptor responsiveness is attenuated from rest to exercise in an exercise intensity-dependent manner. Second, during heavy exercise there is a decrease in the magnitude of vasoconstriction produced by an intra-arterial bolus of a selective α1-agonist compared with rest and mild exercise. These results provide direct evidence that α2-adrenergic-receptor responsiveness in the arterial vasculature of skeletal muscle is attenuated by dynamic exercise. The attenuation of postsynaptic α-adrenergic-receptor responsiveness is a potential mechanism responsible for exercise sympatholysis. In the present study, exogenous activation of α1- and α2-adrenergic receptors produced vasoconstriction during exercise. However, exercise intensity differentially affected the responsiveness of α1- and α2-adrenergic receptors in the arterial vasculature of active skeletal muscle. The vasoconstriction to a selective α2-adrenergic-receptor agonist was attenuated during mild exercise compared with rest and further attenuated by a heavy exercise intensity. In contrast to α2-adrenergic-receptor responsiveness, α1-

**Table 2. Baseline hemodynamic values before clonidine infusion**

<table>
<thead>
<tr>
<th></th>
<th>Control Limb</th>
<th>Experimental Limb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR, beats/min</td>
<td>MAP, mmHg</td>
</tr>
<tr>
<td>Rest</td>
<td>84 ± 4</td>
<td>102 ± 2</td>
</tr>
<tr>
<td>3 miles/h</td>
<td>130 ± 4*</td>
<td>98 ± 3</td>
</tr>
<tr>
<td>6 miles/h and 10% grade</td>
<td>217 ± 8††</td>
<td>113 ± 3</td>
</tr>
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Values are means ± SE. *Significantly different from rest, P < 0.01. †Significantly different from 3 mile/h, P < 0.01.
adrenergic-receptor responsiveness was not attenuated from rest during mild exercise. This is consistent with our laboratory's findings in a previous study in which $\alpha_1$-adrenergic-receptor mediated vasoconstriction to intra-arterial infusion of phenylephrine was unchanged during mild and moderate exercise (4). Including a higher exercise intensity produced the new finding that $\alpha_1$-adrenergic-receptor responsiveness in the skeletal muscle vasculature is attenuated by heavy exercise.

There are several strengths to the experimental protocol used in this study. The use of a conscious animal avoids the confounding effects of anesthesia. Conscious, dynamically exercising dogs allowed natural patterns of muscle recruitment and permitted a higher intensity of exercise than is achievable in anesthetized-animal preparations. This is particularly advantageous because it appears that intense exercise is necessary for attenuation of $\alpha_1$-adrenergic-receptor-mediated vasoconstriction in the arterial vasculature of skeletal muscle. A previous investigation (31) that reported attenuation of $\alpha_2$- but not $\alpha_1$-adrenergic-receptor-mediated vasoconstriction in an anesthetized preparation may not have been able to achieve adequate intensities with electrically stimulated muscle contractions. In addition, intra-arterial infusions of small doses of selective agonists into one hindlimb also provides a distinct advantage by allowing examination of vascular reactivity without confounding changes in systemic hemodynamics. In essence, exogenous activation $\alpha_1$- and $\alpha_2$-adrenergic-receptor-mediated vasoconstriction was examined at rest and during steady-state exercise in a functionally isolated hindlimb. Finally, continuous blood flow measurements are essential given the transient nature of the response to the intra-arterial agonists. We acknowledge that, because measuring bulk blood flow to the hindlimb provides no information regarding distribution of blood flow within the muscle, this experimental protocol cannot provide information regarding the magnitude of vasoconstriction within the various skeletal muscle fiber types of the hindlimb.

An experimental difficulty in assessing vasomotor function using intra-arterial infusions of drugs across widely variable baseline blood flows is drug dilution. Intra-arterial infusions of a constant dose of drug at rest and during exercise result in a decrease in the effective concentration of the agonist through dilution by higher baseline blood flows during exercise. This limitation was addressed as in a previous study (4) by increasing the dose of the drug in direct proportion to the increase in blood flow from rest to exercise. An additional limitation in the present study involves the distribution of $\alpha_2$-adrenergic receptors. $\alpha_2$-Adrenergic receptors are found prejunctionally in proximity to the synapse as well as postjunctionally on vascular smooth muscle. The prejunctional $\alpha_2$-receptor is thought to act in an autoregulatory manner: stimulation of prejunctional $\alpha_2$-receptors by norepinephrine released into the synapse inhibits further release of norepinephrine. To address this limitation, intra-arterial infusions of clonidine were repeated in dogs with a sympathectomized hindlimb. We reasoned that if clonidine administered intra-arterially stimulated prejunctional $\alpha_2$-receptors, vasomotor responses to infusion would differ between intact and sympathectomized limbs. Because there is tonic sympathetic vasoconstriction in active skeletal muscle (2, 4, 12, 27, 26), any prejunctional inhibition of norepinephrine release by clonidine would offset the postjunctional actions on the vascular smooth muscle. In the sympathectomized hindlimb though, the magnitude of vasoconstriction would be greater because the postjunctional effects of clonidine would be unopposed. The fact that clonidine infusion...
caused similar magnitudes of vasoconstriction in intact and sympathectomized limbs indicates that the primary effect of clonidine infused intra-arterially was to stimulate postjunctional $\alpha_2$-receptors.

During exercise, blood flow to active skeletal muscle is substantially elevated compared with the blood flow levels seen at rest. It could be argued that the diminished response to sympathetic stimulation seen during exercise is the result of a nonspecific elevation in blood flow rather than being distinctly related to exercise. There are two pieces of evidence that argue against this idea. First, Thomas et al. (31) pharmacologically elevated blood flow in the absence of skeletal muscle contractions and observed no attenuation of vasoconstriction to sympathetic nerve stimulation. Second, data from our own laboratory have shown no attenuation in $\alpha_2$-adrenergic-receptor vasoconstriction in active skeletal muscle when blood flow was elevated during mild to moderate exercise (4). Therefore, we believe it is unlikely that the elevation in blood flow alone is responsible for sympatholysis.

Sympatholysis, manifested as diminished skeletal muscle vasoconstriction to direct stimulation of the sympathetic nerves or administration of exogenous vasoconstrictor substances, has been shown in a number of studies (5, 13, 28, 29, 31, 32). However, the topic is somewhat controversial. The results from the present study provide evidence that an exercise-induced alteration in postjunctional $\alpha$-adrenergic-receptor responsiveness is a potential mechanism of exercise sympatholysis. However, there may also be a component of sympatholysis that is explained through a prejunctional mechanism (6). Burcher and Garlick (5) hypothesized that a prejunctional mechanism leading to decreased release of neurotransmitter was involved in exercise sympatholysis because of the greater attenuation of vascular responsiveness to sympathetic stimulation compared with intra-arterial norepinephrine during muscle contraction. Although examination of a prejunctional mechanism was beyond the scope of this study, it must be recognized that reductions in neurotransmitter release may play a role in sympatholysis.

In the present study $\alpha_2$-adrenergic-receptor-mediated vasoconstriction was attenuated in an exercise intensity-dependent manner. Two previous studies (1, 31) have reported attenuation of $\alpha_2$-adrenergic-receptor-mediated vasoconstriction in the arterial vasculature of skeletal muscle during muscle contractions in the anesthetized rat. However, ours is the first study to show this phenomenon in a conscious animal during dynamic exercise. A decrease in $\alpha_2$-adrenergic-receptor responsiveness may play a prominent role in exercise sympatholysis due to a heterogeneous distribution of postsynaptic $\alpha_1$- and $\alpha_2$-adrenergic receptors in the arterial vasculature of skeletal muscle. Faber (9) demonstrated that both $\alpha_1$- and $\alpha_2$-adrenergic receptors are present on large arterioles but that only $\alpha_2$-receptors exist on the terminal arterioles. In response to sympathetic stimulation, $\alpha_1$-adrenergic receptors appear to exert the predominant control over the diameter of the large arterioles, whereas $\alpha_2$-receptors control the diameter of the terminal arterioles (24). In addition, $\alpha_2$-adrenergic-receptor-mediated vasoconstriction appears to be particularly sensitive to changes in the chemical environment within muscle that may occur during exercise. Postsynaptic $\alpha_2$-adrenergic-receptor-mediated vasoconstriction is sensitive to and attenuated by modest reductions in pH (19, 21, 30), hypoxia (19, 30), and ischemia (20). In contrast, $\alpha_1$-adrenergic-receptor-mediated vasoconstriction appears to be unaffected by changes in pH (19, 30), hypoxia (19, 30), or ischemia (20). The differential distribution and sensitivity of $\alpha$-adrenergic-receptors undoubtedly contributes substantially to exercise sympatholysis. The functional importance of alterations in $\alpha$-adrenergic receptor responsiveness may be to provide a selective means of directing blood flow to areas of high metabolic activity in active skeletal muscle during exercise.

The appropriate expression of data concerning vasomotor function has led to some of the controversy in the literature regarding the issue of sympatholysis. Indeed, opposite conclusion can be made, depending on the method used to express changes in vasomotor function (4, 13, 25, 26, 32). Unfortunately, despite the linear relationship between vascular conductance and blood flow (17, 25), the less appropriate measurement of vascular resistance is often used. In addition, changes in vasomotor function from baseline can be expressed as either an absolute change or a percent change. Rowlands and Donald (29) noted that, when expressing changes in vascular tone from baseline, the percent change is more appropriate than the absolute change. This is particularly important in the present study in comparing the magnitude of vasoconstriction (and therefore change in the radius of the vessel) produced by $\alpha$-adrenergic agonists across widely different baseline flows. Despite differing baseline blood flows, a given percent reduction in conductance will always reflect a predictable percent reduction in the radius of the vessel. For example, it can be calculated that a 16% decrease in vessel radius will result in a 50% reduction in conductance and that a 50% decrease in vessel radius will result in a 94% reduction in conductance. On the other hand, absolute changes in conductance can vary considerably when identical percent changes in vessel radius are imposed on differing baseline blood flows. The percent change in conductance has a predictable relationship with change in radius of the vessel, whereas the absolute change does not and can lead to inappropriate conclusions. Therefore, if the desire is to compare the degree of vasoconstriction in a vascular bed, which by definition reflects a change in radius, the percent change in conductance more accurately describes these changes. Thus, in the present study, we conclude that intra-arterial infusion of clonidine into the arterial vasculature of active skeletal muscle produced less vasoconstriction during mild and heavy steady-state exercise than at rest. Furthermore, we conclude that intra-arterial infusion of phenylephrine into the arterial vasculature of skeletal muscle produced the same degree of vasoconstriction during mild...
exercise as at rest but was attenuated during heavy exercise.

The results from the present study reveal that α₂-adrenergic-receptor responsiveness in the arterial vasculature of skeletal muscle is attenuated from rest to exercise in an exercise intensity-dependent manner. However, α₁-adrenergic-receptors in the arterial vasculature of skeletal muscle are more resistant to inhibition and there is attenuation of α₁-adrenergic-receptor-mediated vasoconstriction only during heavy exercise. The functional importance of exercise sympatholysis may be to provide a selective means of directing blood flow to areas of high metabolic activity in active skeletal muscle during exercise.

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REFERENCES