Short-term exercise training augments sympathetic vasoconstrictor responsiveness and endothelium-dependent vasodilation in resting skeletal muscle

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Jendzjowsky NG, DeLorey DS. Short-term exercise training augments sympathetic vasoconstrictor responsiveness and endothelium-dependent vasodilation in resting skeletal muscle. Am J Physiol Regul Integr Comp Physiol 303: R332–R339, 2012. First published June 13, 2012; doi:10.1152/ajpregu.00053.2012.—We tested the hypothesis that 4 wk of exercise training would diminish the magnitude of vasoconstriction in response to sympathetic nerve stimulation and augment endothelium-dependent vasodilation (EDD) in resting skeletal muscle in a training intensity-dependent manner. Sprague-Dawley rats were randomly assigned to sedentary time-control (S), mild- (M; 20 m/min, 5% grade), or heavy-intensity (H; 40 m/min, 5% grade) treadmill exercise groups. Animals trained 5 days/wk for 4 wk with training volume matched between groups. Rats were anesthetized and instrumented for study 24 h after the last training session. Arterial pressure and femoral artery blood flow were measured, and femoral vascular conductance (FVC) was calculated. Lumbar sympathetic chain stimulation was delivered continuously at 2 Hz and in patterns at 20 and 40 Hz. EDD was assessed by the vascular response to intra-arterial bolus injections of ACh. The response (% change FVC) to sympathetic stimulation increased (P < 0.05) in a training intensity-dependent manner at 2 Hz (S: −20.2 ± 9.8%, M: −34.0 ± 6.7%, and H: −44.9 ± 2.0%), 20 Hz (S: −22.0 ± 10.6%, M: −31.2 ± 8.4%, and H: −42.8 ± 5.9%), and 40 Hz (S: H: −24.5 ± 8.5%, M: −35.1 ± 8.9%, H: −44.9 ± 6.5%). The magnitude of EDD also increased in a training intensity-dependent manner (P < 0.05). These data demonstrate that short-term exercise training augments the magnitude of vasoconstriction in response to sympathetic stimulation and EDD in resting skeletal muscle in a training intensity-dependent manner.

sympathetic nervous system; nitric oxide; exercise intensity; blood flow

THE PRECISE REGULATION of arterial tone is necessary for the maintenance of systemic arterial blood pressure and the adequate delivery of blood flow and oxygen to vital organs and tissues. Arterial tone is regulated by a dynamic balance between sympathetic nervous system-mediated vasoconstriction, myogenic tone, and local vasodilator signaling (45). At rest, the skeletal muscle vascular bed receives a substantial portion of cardiac output and, therefore, is responsible for the maintenance of a large portion of systemic vascular resistance and systemic arterial blood pressure.

Efferent sympathetic nerve activity is characterized by random bursts of activity, followed by periods of quiescence. In humans and animals, there is continuous low-frequency nerve discharge at rest, with an average firing frequency of ~1 Hz (37). However, during physiological stress, such as exercise, the burst frequency of sympathetic nerve discharge increases, with intraburst single nerve discharge frequencies of 20–50 Hz (23, 26, 37). The frequency and pattern of efferent sympathetic nerve activity influence the amount and type of neurotransmitter released (4, 11, 12, 18, 22, 26, 42). Low-discharge frequencies lead to adenosine 5′-triphosphate (ATP) release followed by norepinephrine (NE), whereas midrange discharge frequencies produce both NE and ATP release, while high-discharge frequencies favor the release of neuropeptide Y (NPY) (26). As such, sympathetic vasoconstriction is mediated by the relative contributions of NE and the sympathetic cotransmitters ATP and NPY. Our laboratory (14) and others (4–10, 22, 26, 43, 44) have demonstrated that NE, ATP, and NPY each contribute to vasoconstriction in the skeletal muscle vascular bed, and their contribution to the overall regulation of arterial tone varies with aging (13), exposure to hypoxia (12, 23, 26), and exercise (5–8).

Chronic endurance exercise training has been repeatedly shown to enhance skeletal muscle vasodilation (16, 17, 19, 24, 27, 33, 34, 39, 52) and increase skeletal muscle blood flow capacity (1, 32). A consistent vascular adaptation associated with exercise training is an increase in endothelium-dependent vasodilation (EDD) (17, 19, 27, 34, 52). However, vascular control mechanisms operate in an integrative manner, and as such, adaptations to exercise training are unlikely to occur in isolation. Whether training-induced changes in vasodilator function affect the regulation of skeletal muscle sympathetic vasoconstriction has not been clearly established. Indeed, aerobic endurance exercise training has been shown to increase (41), decrease (20, 48), or have no effect (47) on efferent muscle sympathetic nerve activity. Furthermore, postsynaptic α-adrenergic receptor responsiveness has been shown to be increased (28), decreased (17, 19, 49, 55), or unchanged (24, 52) following chronic endurance exercise training. In summary, the available scientific literature related to the effect of exercise training on the regulation of skeletal muscle sympathetic vasoconstriction is limited and contradictory.

In addition to a lack of understanding of the effects of exercise training on the regulation of sympathetic vasoconstriction, our understanding of training stimulus responsible for producing vascular adaptations is limited. Indeed, vascular adaptations to exercise training have been demonstrated in response to training paradigms of various durations and intensities (16, 17, 19, 24, 27, 33, 34, 39, 52). To the authors’ knowledge, the relationship between the intensity of exercise training and sympathetic vasoconstriction and EDD has not been studied.
Table 1. Cardiovascular and metabolic indices of training efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Mass, g</th>
<th>Heart Mass, g</th>
<th>Heart-Body Mass Ratio</th>
<th>Soleus Citrate Synthase Activity, μmol-min protein$^{-1}$·mg$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary ($n = 13$)</td>
<td>445 ± 30</td>
<td>1.5 ± 0.2</td>
<td>0.34 ± 0.06</td>
<td>34 ± 15</td>
</tr>
<tr>
<td>Mild-intensity ($n = 12$)</td>
<td>422 ± 31</td>
<td>1.7 ± 0.2†</td>
<td>0.40 ± 0.05†</td>
<td>49 ± 12†</td>
</tr>
<tr>
<td>Heavy-intensity ($n = 11$)</td>
<td>393 ± 20†</td>
<td>1.8 ± 0.2†</td>
<td>0.45 ± 0.05†‡</td>
<td>48 ± 9†</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD with group sample sizes in parentheses. †Significant difference from the sedentary control group. ‡Significant difference between mild- and heavy-intensity trained groups. A $P$ value < 0.05 was considered statistically significant.

With this background, the purpose of the present study was to investigate the effects of 4 wk of mild- and heavy-intensity exercise training on 1) the magnitude of vasoconstriction in response to stimulation of the lumbar sympathetic chain and 2) EDD in the resting skeletal muscle vascular bed. The lumbar sympathetic chain was stimulated with different patterns of impulses that have been shown to evoke the preferential, but not the exclusive, release of NE (2 Hz continuous), ATP (bursts of impulses at 20 Hz), and NPY (bursts of impulses at 40 Hz) (23, 37, 40). It was hypothesized that exercise training would diminish the magnitude of sympathetic vasoconstriction and augment EDD in a manner dependent on the intensity of exercise training.

METHODS

Animals and animal care. A total of 45 male Sprague-Dawley rats (~2 mo old) were obtained from the institutional animal colony. Rats were housed in pairs in a 12:12-h light-dark cycle, environmentally controlled (22–24°C, 40–70% humidity) room. Water and rat chow (Lab Diet 5001, PMI Nutrition, Brentwood, MO) were provided ad libitum. All experiments were conducted in accordance with the Canadian Council on Animal Care Guidelines and Policies with approval from the Animal Care and Use Committee: Health Sciences for the University of Alberta.

Exercise training. All rats were habituated to the laboratory and exercise by running on a treadmill (Panlab LE8710; Panlab, Barcelona, Spain) 10 min a day for 5 days at 10 m/min, 0% grade. At this point, four rats were removed from the study because of an inability to run voluntarily. After familiarization, rats were randomly assigned to three groups: 1) sedentary time-control (S), 2) mild-intensity exercise training (M; 20 m/min, at 5% grade), or 3) heavy-intensity exercise training (H; 40 m/min, at 5% grade). Randomization was achieved by selecting one of three labeled chips (sedentary, mild, or heavy) from a bag for each rat. Exercise training was performed 5 days/wk for 4 wk. The S group was handled and weighed daily. Immediately following familiarization, the M group ran at 20 m/min at 5% grade for 600 m and maintained this intensity for the duration of the exercise program. The H group began running at 40 m/min at 5% grade, starting with 15 intervals of 1 min of running and 1 min of rest. Each day, interval run time was increased, while rest time was maintained at 1 min until each animal was able to run continuously at 40 m/min at 5% grade for 600 m; this was achieved within 11 ± 2 days, as described previously (25). Animals in each training group ran the same distance (600 m) at their assigned treadmill speed in each training bout. Thus, the total volume of work was matched between groups allowing the effect of exercise training intensity to be isolated.

Instrumentation. Twenty-four hours after the last training session, rats were anesthetized with inhalation of isoflurane (3.5%, balance O2). The right jugular vein was then cannulated, and anesthesia was maintained with α-chloralose (8–16 mg·kg$^{-1}$·h$^{-1}$) and urethane (50–100 mg·kg$^{-1}$·h$^{-1}$). The depth of anesthesia was assessed by the stability of arterial blood pressure, heart rate (HR), and the absence of a withdrawal reflex in response to a painful stimulus (i.e., paw-pinch). A tracheotomy was performed to facilitate spontaneous respiration, and the left brachial artery was cannulated and connected to a solid state pressure transducer (Abbott, North Chicago, IL) for continuous measurement of arterial blood pressure. The left femoral artery and vein were cannulated for the delivery of pharmacology. Blood flow was measured using a flow probe (0.7 V; Transonic Systems T107, Ithaca, NY), placed around the right femoral artery, and connected to a flowmeter (T106 Transonic Systems). Core temperature was monitored by rectal probe and maintained at 36–37°C by external heating pad (Physitemp, TCAT-2, Clifton, NJ).

Lumbar sympathetic chain stimulation. Through a laparotomy, a bipolar silver-wire stimulating electrode was attached to the lumbar sympathetic chain between L3 and L4. The electrodes were secured in place and electrically isolated by embedding them in a rapidly curing balance O2). The right jugular vein was then cannulated, and anesthesia was maintained with α-chloralose (8–16 mg·kg$^{-1}$·h$^{-1}$) and urethane (50–100 mg·kg$^{-1}$·h$^{-1}$). The depth of anesthesia was assessed by the stability of arterial blood pressure, heart rate (HR), and the absence of a withdrawal reflex in response to a painful stimulus (i.e., paw-pinch). A tracheotomy was performed to facilitate spontaneous respiration, and the left brachial artery was cannulated and connected to a solid state pressure transducer (Abbott, North Chicago, IL) for continuous measurement of arterial blood pressure. The left femoral artery and vein were cannulated for the delivery of pharmacology. Blood flow was measured using a flow probe (0.7 V; Transonic Systems T107, Ithaca, NY), placed around the right femoral artery, and connected to a flowmeter (T106 Transonic Systems). Core temperature was monitored by rectal probe and maintained at 36–37°C by external heating pad (Physitemp, TCAT-2, Clifton, NJ).

Following surgical instrumentation, a ~20-min recovery period was utilized to allow all hemodynamic variables to stabilize, and the following experiments were conducted. Five rats died during surgical instrumentation.

The effects of short-term mild- and heavy-intensity exercise training on endothelium-dependent vasodilatation ($S$, $n = 13$; $M$, $n = 12$; $H$, $n = 11$). To investigate the effect of exercise training on EDD, the magnitude of vasodilatation in response to intra-arterial bolus injections of ACh (0.005, 0.05, 0.1, 0.25, and 0.5 μg) was assessed. A 5-min resting period interspersed each injection. To minimize any flow-induced vasodilatation during intra-arterial injections, small boluses (100 μl) of drug were injected over ~5 s. Vehicle injections at this volume and rate did not increase hind-limb blood flow.

Table 2. Baseline hemodynamics

<table>
<thead>
<tr>
<th>Group</th>
<th>HR, bpm</th>
<th>MAP, mmHg</th>
<th>FBF, ml/min</th>
<th>FVC, ml·min$^{-1}$·mmHg$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary ($n = 13$)</td>
<td>400 ± 27</td>
<td>99 ± 13</td>
<td>3.5 ± 1.1</td>
<td>0.036 ± 0.014</td>
</tr>
<tr>
<td>Mild-intensity ($n = 12$)</td>
<td>354 ± 35†</td>
<td>92 ± 14†</td>
<td>3.4 ± 0.6</td>
<td>0.038 ± 0.008</td>
</tr>
<tr>
<td>Heavy-intensity ($n = 11$)</td>
<td>366 ± 32†</td>
<td>90 ± 15†</td>
<td>3.4 ± 0.8</td>
<td>0.039 ± 0.011</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD with group sample sizes in parentheses. A $P$ value < 0.05 was considered statistically significant. Heart rate (HR), mean arterial blood pressure (MAP), femoral blood flow (FBF), and femoral vascular conductance (FVC). †Significant difference from the sedentary control group.
The effects of short-term mild- and heavy-intensity exercise training on the response to lumbar sympathetic chain stimulation (S, n = 13; M, n = 12; H, n = 11). The vasoconstrictor response evoked by stimulation of the lumbar sympathetic chain was determined. Stimulation patterns included 1) continuous stimulation at 2 Hz; 2) 20-Hz bursts for 1 s repeated every 10 s and; 3) 40-Hz bursts for 0.5 s repeated every 10 s. During each 1-min stimulation period, a total of 120 1-ms impulses were delivered at 1 mAmp. Sympathetic stimulations were delivered in random order and were separated by at least 5 min to allow restoration of baseline hemodynamics between stimulations. The stimulation patterns were designed to be reflective of a low resting level of MSNA and moderate- and high-frequency bursts of MSNA that occur in response to physiological stress, such as exercise (40).

Assessment of training efficacy. Upon completion of all experiments, animals were euthanized by anesthetic overdose, and the heart and soleus muscle were dissected free. Heart mass and soleus muscle citrate synthase activity were determined and used as indicators of the efficacy of exercise training. Citrate synthase activity was measured according to the method of Srere (50) and normalized for total protein concentration of the tissue sample, as determined by a Bradford protein assay kit.

Drugs. All drugs were purchased from Sigma-Aldrich (Oakville, ON, Canada) and dissolved in 0.9% physiological saline.

Data analysis. Data were recorded using Chart 7 data acquisition software (AD Instruments Colorado Springs, CO). Arterial blood pressure and femoral artery blood flow (FBF) were recorded continuously at 100 Hz. HR was derived from the arterial blood pressure waveform, and femoral vascular conductance (FVC) was calculated. The magnitude of vasoconstriction in response to sympathetic stimulation was calculated as the difference between the integral of FVC during the 1-min lumbar sympathetic chain stimulation period and the integral of 1 min of the FVC baseline preceding the stimulation and was expressed as a percent change from the FVC baseline (data shown in Fig. 2; S, n = 13, M, n = 12, H, n = 11). The response to ACh was calculated as the difference between the peak FVC response (~3 s average) and the preinfusion baseline (~20 s average) and was expressed as a percentage change from the FVC baseline (Fig. 3; S, n = 13, M, n = 12, H, n = 11). All data were expressed as means ± SD.

The effect of exercise training on body and cardiac mass, citrate synthase activity, and the response to ACh were determined by one-way ANOVA. The effect of exercise training on the response to sympathetic stimulation was determined by two-way repeated-measures ANOVA (SigmaPlot 11 Systat, Richmond, CA). When significant F ratios were found, Student-Newman-Keuls post hoc analysis was performed. The relationship between endothelium-dependent vasodilation (FVC, % change in response to 0.1 μg ia ACh injection) and the response to continuous and patterned sympathetic stimulations (FVC, % change) was assessed with Pearson product moment correlation. A P value <0.05 was considered statistically significant.

RESULTS

All rats randomized to exercise training groups completed the prescribed training regimen.

On completion of the exercise training protocols, body mass was lower in exercise-trained compared with sedentary time-control rats (P < 0.05). Heart mass was greater in exercise-trained compared with sedentary time-control rats (P < 0.05), and the heart mass-body mass ratio was increased in a training intensity-dependent manner (Table 1, P < 0.05). Soleus muscle citrate synthase activity was also greater in exercise-trained compared with sedentary time-control rats (Table 1, P < 0.05).
Basal HR and mean arterial blood pressure were lower \( (P < 0.05) \) in exercise-trained compared with the sedentary time-control rats, whereas basal FBF and FVC were similar in all groups (Table 2).

**Effect of exercise training on the response to sympathetic stimulation.** The responses to lumbar sympathetic stimulation delivered continuously at 2 Hz and in bursting patterns at 20 and 40 Hz in a representative animal are illustrated in Fig. 1. Each pattern of sympathetic stimulation produced a similar vasoconstriction in S, M, and H groups. However, the magnitude of vasoconstriction in response to sympathetic stimulation delivered continuously at 2 Hz and in patterns at 20 and 40 Hz was increased as a function of training intensity (Fig. 2 and Table 3).

**Effects of exercise training on endothelium-dependent vasodilation.** Short-term exercise training enhanced EDD in a manner dependent on the intensity of exercise training (Fig. 3, \( P < 0.05 \)).

**Relationship between the vascular response to dilator and constrictor stimuli.** The magnitude of EDD (vasodilation to 0.1 \( \mu \)g ACh) was correlated with the magnitude of vasoconstriction in response to lumbar sympathetic chain stimulations delivered continuously at 2 Hz \( (r = 0.602; P < 0.001) \) and in bursting patterns at 20 \( (r = 0.619; P < 0.001) \) and 40 Hz \( (r = 0.601; P < 0.001) \).

**DISCUSSION**

The purpose of this study was to investigate the effects of short-term, mild- and heavy-intensity exercise training on the magnitude of vasoconstriction in response to sympathetic stimulation and EDD in resting skeletal muscle. The primary new findings from this study were that 1) short-term exercise training augmented the magnitude of vasoconstriction in response to sympathetic stimulation and EDD in a manner dependent on the intensity of training and 2) the exercise-training mediated increases in sympathetic vascular responsiveness was significantly correlated with EDD.

**Sympathetic vasoconstriction to lumbar sympathetic chain stimulation.** The magnitude of vasoconstriction in response to all patterns of sympathetic stimulation was increased in exercise-trained rats compared with sedentary time-controls as a function of training intensity. The response to sympathetic stimulation may be altered by an increased expression or an enhanced responsiveness of postsynaptic receptors. To date, investigations of the effects of exercise training on the expression of postsynaptic receptors in the skeletal muscle vasculature have not been completed. Previous studies of the effect of exercise training on postsynaptic receptor responsiveness have utilized a variety of experimental models and training paradigms and have produced conflicting results \( (17, 19, 24, 28, 34, 49, 55) \). An important strength of the present study was the isolation of the effects of exercise-training intensity on vascular control by matching the total volume of work completed at each training intensity. To our knowledge, this is the first study to demonstrate a dose-response relationship between the intensity of exercise training and the response to sympathetic stimulation. However, previous studies that have used heavy-intensity exercise training to investigate the effects of training on vascular responsiveness have demonstrated an enhanced vasoconstriction in response to sympathetic stimulation following training \( (34, 39) \), suggesting that training-induced adaptations may be, in part, dictated by the intensity of exercise training.

The overall duration of the training program may also influence the effects of exercise training on vascular function. Exercise training-induced vascular adaptations appear to occur in phases, where functional (i.e., vasoreactivity) changes occur during the early portion of a training program and are followed by structural adaptations (i.e., vessel growth and vascular remodeling) as training is continued \( (15, 21) \). We suggest that
the short-term training duration employed in the present study may reveal early functional changes in the responsiveness of the hind-limb vascular bed as the length of training necessary to develop and sustain angiogenic growth, and develop vascular remodeling appears to be greater than 4 wk (15, 21).

Studies that have utilized short-term training durations (1–6 wk) have reported unchanged (52), reduced (55), or enhanced (39) responsiveness to NE following exercise training. Following very mild- to mild-intensity treadmill training, the response to NE was not altered in isolated gracilis muscle first-order arterioles (52). Whereas, swim training in rats reduced the response to NE in gastrocnemius muscle (34). In contrast, 90 min of daily moderate-intensity sprint-interval training enhanced the response to NE in gastrocnemius muscle (52). Whereafter, in a porcine training study, 7 days of heavy-intensity treadmill exercise training enhanced the response to NE in the abdominal aorta (17, 49). Studies that have utilized short-term training durations (1–6 wk) have reported unchanged (52), reduced (55), or enhanced (39) responsiveness to NE following exercise training. Following very mild- to mild-intensity treadmill training, the response to NE was not altered in isolated gracilis muscle first-order arterioles (52). Whereas, swim training in rats reduced the response to NE in gastrocnemius muscle (34). In contrast, 90 min of daily moderate-intensity sprint-interval training enhanced the response to NE in gastrocnemius muscle (52). Whereafter, in a porcine training study, 7 days of heavy-intensity treadmill exercise training enhanced the response to NE in the abdominal aorta (17, 49).

Endothelium-dependent vasodilation. A consistent vascular adaptation associated with exercise training is an enhanced EDD (16, 17, 19, 24, 27, 33, 34, 39, 52). In agreement with previous findings (16, 17, 19, 24, 27, 33, 34, 39, 52), EDD was augmented following exercise training in the present study. A variety of exercise training paradigms ranging from mild-intensity continuous training to heavy-intensity sprint-interval training have been shown to enhance EDD (16, 17, 27, 34, 52). However, to our knowledge, the present study is the first to demonstrate a training intensity-dependent upregulation of EDD.

In response to acute progressive exercise, shear rate has been shown to increase as a function of exercise intensity (56) and an exercise-induced increase in shear rate has been shown to be the primary mechanism for the improved EDD following exercise training (53). We were unable to measure shear rate during exercise training in the present study; however, a greater shear rate during heavy-intensity compared with mild-intensity exercise training would be expected. Thus, the present findings suggest that a training intensity-dependent increase in shear rate may lead to a proportional increase in EDD. Consistent with this notion, endothelial nitric oxide synthase expression has been shown to increase as a function of shear rate in cultured endothelial cells exposed to different levels of shear stress (35, 54).

The training intensity-dependent improvement of EDD may also be related to skeletal muscle recruitment. It is well established that there is a progressive recruitment of additional muscle fibers during progressive exercise and that skeletal muscle blood flow is closely matched to skeletal.

Table 3. The resting skeletal muscle vascular response to sympathetic stimulation

<table>
<thead>
<tr>
<th>Stimulation Pattern, Hz</th>
<th>Group</th>
<th>MAP</th>
<th>FBF</th>
<th>FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Sedentary (n = 13)</td>
<td>2.9 ± 5.2</td>
<td>-0.7 ± 0.4</td>
<td>-0.007 ± 0.004*</td>
</tr>
<tr>
<td></td>
<td>Mild-intensity (n = 12)</td>
<td>6.2 ± 5.7</td>
<td>-0.9 ± 0.4</td>
<td>-0.013 ± 0.005*</td>
</tr>
<tr>
<td></td>
<td>Heavy-intensity (n = 11)</td>
<td>5.9 ± 3.4</td>
<td>-1.5 ± 0.6</td>
<td>-0.018 ± 0.008*</td>
</tr>
<tr>
<td>20</td>
<td>Sedentary (n = 13)</td>
<td>3.3 ± 5.4</td>
<td>-0.8 ± 0.5</td>
<td>-0.008 ± 0.005*</td>
</tr>
<tr>
<td></td>
<td>Mild-intensity (n = 12)</td>
<td>6.5 ± 4.7</td>
<td>-1.0 ± 0.5</td>
<td>-0.012 ± 0.005*</td>
</tr>
<tr>
<td></td>
<td>Heavy-intensity (n = 11)</td>
<td>9.1 ± 3.4</td>
<td>-1.5 ± 0.5</td>
<td>-0.019 ± 0.007*</td>
</tr>
<tr>
<td>40</td>
<td>Sedentary (n = 13)</td>
<td>3.5 ± 6.6</td>
<td>-0.9 ± 0.6</td>
<td>-0.009 ± 0.005*</td>
</tr>
<tr>
<td></td>
<td>Mild-intensity (n = 12)</td>
<td>8.7 ± 3.7</td>
<td>-0.9 ± 0.3</td>
<td>-0.013 ± 0.004*</td>
</tr>
<tr>
<td></td>
<td>Heavy-intensity (n = 11)</td>
<td>9.1 ± 4.0</td>
<td>-1.5 ± 0.6</td>
<td>-0.020 ± 0.007*</td>
</tr>
</tbody>
</table>

Values are expressed as means ± SD. A P value <0.05 was considered to be statistically significant. Absolute changes in integrated units for MAP, FBF, and FVC. *Significant difference between all groups. †Significant difference from the sedentary control group. ‡Significant difference between mild- and heavy-intensity-trained groups.
muscle recruitment (30, 31). Therefore, it is conceivable that a larger proportion of the hind-limb skeletal muscle vascular bed was exposed to increased shear rates during heavy- compared with mild-intensity exercise training. Thus, the potential exists that the intensity-dependent increase of EDD in exercise-trained animals reflects the collective vasodilation of a greater number of conditioned vessels in heavy-intensity compared with mild intensity-trained and sedentary rats.

**Relationship between the vascular response to dilator and constrictor stimuli.** In a study of middle-aged men, Sugawara et al. (51) reported that following 3 mo of aerobic exercise training, an enhanced EDD was offset by a parallel increase in sympathetic vasoconstriction. NE spillover was increased following training in the study of Sugawara et al. (51), suggesting that the increased sympathetic vasoconstriction was the result of a training-induced increase in basal sympathetic outflow. In the present study, the magnitude of vasoconstriction in response to sympathetic stimulation at each frequency was correlated with the magnitude of EDD in all rats. Collectively, the present findings suggest that an increase in the response to sympathetic nerve activity may offset a training-induced increase in EDD to maintain basal hemodynamics.

**Experimental considerations and limitations.** A major strength of the current experimental approach is the ability to study the dynamic regulation of sympathetic vasoconstriction in an intact vascular bed as the reactivity of a single vascular segment may not be reflective of the control of an entire vascular bed. We were also able to directly stimulate the lumbar sympathetic chain and induce the release of endogenous neurotransmitters in the present study. A limitation of the assessment of sympathetic vascular reactivity in the intact hind-limb skeletal muscle vascular bed is that the assessment of blood flow distribution between and within muscles was not possible. Another potential limitation of the present study was the use of juvenile aged rats (~2 mo of age at onset of training). Although these animals were sexually mature, exercise training occurred during a period of growth and development when vascular growth factors may have influenced vascular responsiveness (36, 46). However, we believe the inclusion of a sedentary time-control group minimized any confounding effects related to vascular growth and development.

**Perspectives and Significance**

Chronic endurance exercise training is generally associated with positive adaptations in vascular function. However, our knowledge of the training paradigm (i.e., the prescription of exercise intensity, frequency, and duration) that produces changes in vascular function and the time course of vascular adaptations in response to training are limited. The findings from the present study indicate that as little as 4 wk of chronic endurance exercise training augments EDD and vasoconstriction to sympathetic stimulation in a training intensity-dependent manner. We believe that the present data demonstrate that training-induced adaptations to one signaling pathway do not occur in isolation but likely occur concurrently with other adaptations that are integrated by the vascular smooth muscle. We suggest that future investigations should focus on the dose-response relationship between exercise training and integrated vascular adaptations.

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SYMPATHETIC VASOCONSTRICTION FOLLOWING EXERCISE TRAINING

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


