Systemic α-adrenergic and nitric oxide inhibition on basal limb blood flow: effects of endurance training in middle-aged and older adults

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AN ACUTE BOUT OF EXERCISE induces several types of stresses, yet when performed chronically, it confers protection against many chronic diseases including atherosclerosis. One of these stresses, shear stress, can rise during exercise as a result of increased blood flow to the working muscles, and in response, the endothelium releases a number of vasoactive substances including nitric oxide (NO).

NO bioavailability and its stimulated release decrease with advancing age (4, 36), and it is associated with reductions in limb blood flow and vascular conductance (5, 7). It is now well established that impaired endothelium-dependent vasodilation is an early manifestation of atherosclerosis and is associated with overt coronary artery disease (29). Fortunately, regular endurance exercise training appears to increase the basal production of NO and its bioavailability in older adults. A cross-sectional study (36) reported that the decreases in forearm blood flow with the NO synthase (NOS) inhibitor Nω-monomethyl-L-arginine (L-NMMA) were significantly greater in well-trained elderly people compared with that in age-matched sedentary controls. A recent intervention study reported that resting plasma concentrations of nitrite/nitrate (NOx), the stable end product of NO, and cGMP, a second messenger of NO, significantly increased after 3 mo of moderate aerobic exercise training in sedentary older women (17).

Given the important role of NO in modulating vascular tone and perfusion, it is reasonable to hypothesize that the improvements in basal NO release and bioavailability with exercise training would increase basal limb blood flow; however, this does not appear to be the case (8, 19). This finding has led us to postulate that there may be some physiological changes that are interacting antagonistically with basal NO release. In this context, the age-associated reductions in basal limb blood flow and vascular conductance are mediated by chronically augmented α-adrenergic vasoconstriction, and basal sympathetic nerve activity is elevated in older endurance-trained adults (5, 7). Therefore, enhanced NO bioavailability may oppose the increase in sympathetic vasoconstriction, resulting in no change in basal limb blood flow with exercise training. Indeed, Skarphedinsson et al. (30) have previously reported that muscle sympathetic nerve activity is positively associated with a plasma marker of NO bioavailability.

Accordingly, the primary aim of the present study was to determine the effects of endurance training on the modulation of basal limb blood flow by α-adrenergic vasoconstriction and NO release in middle-aged and older adults. We hypothesized that basal limb blood flow would not change with aerobic exercise training and that the lack of change in blood flow is related to the augmented endothelium function and the associated increases in sympathetic vasoconstrictor tone.

METHODS

Subjects

Seven sedentary but apparently healthy middle-aged and older adults [60 ± 3 yr, 2 men and 5 postmenopausal (i.e., estrogen...
deficient) women] were studied. Middle-aged adults were included in this study because basal femoral blood flow and vascular conductance decrease linearly with advancing age, and middle-aged adults, irrespective of gender, already exhibit age-related declines in basal limb perfusion (5, 7, 23). Subjects who were current smokers or smoked within the past 2 yr, who took medications (including hormone replacement therapy), or who had significant intima-media thickening (>1.0 mm), plaque formation, and/or other characteristics of atherosclerosis (e.g., ankle-brachial index <0.9, Ref. 3) were excluded. None of the subjects had engaged in regular physical activity (>2/week) or exercise training program in the past 1 yr, which was verified through the questionnaire. All subjects had no apparent cardiovascular disease as assessed by medical history and physical examination. This study was reviewed and approved by the Institutional Review Board at the University of Tsukuba. All potential risks and procedures of the study were explained to the subjects, and they gave their written informed consent to participate in the study.

**Experimental Protocol**

All measurements were performed after an abstinence of caffeine and an overnight fast. Subjects were studied under supine resting conditions in a quiet, temperature-controlled room (24–26°C). All the posttraining measurements were performed at least 48 h after the last exercise bout to avoid the acute (i.e., residual) effect of exercise on major dependent variables. A timeline of the experimental protocol is illustrated in Fig. 1. The main hemodynamic measurements were performed three times: at baseline, with systemic α-adrenergic blockade, and with the combined systemic α-adrenergic blockade and systemic NOS inhibition as previously described by Halliwill et al. (13). After the subject had 15 min of supine rest, baseline measurements were made. After this, systemic α-adrenergic blockade [phentolamine mesylate, 0.1428 mg·kg⁻¹·bolus over 2 min and a subsequent continuous (0.01428 mg·kg⁻¹·min⁻¹) intravenous infusion] was administered. The second set of measurements was performed 10 min after the commencement of continuous phentolamine infusion. Subsequently, subjects underwent systemic NOS inhibition [L-NMMA, 3 mg/kg iv bolus over 5 min and a subsequent continuous (0.05 mg·kg⁻¹·min⁻¹) intravenous infusion] while under α-adrenergic blockade. The final measurements were performed 10 min after the commencement of continuous L-NMMA infusion. The infusion procedures and drug dosages were based on previous studies employing systemic administration of phentolamine (13) and L-NMMA (18, 31, 33) that have reported adequate blockade of α-adrenergic activity and NO production with this protocol. Because systemic L-NMMA administration does not influence local muscle bed sympathetic nervous system activity (25), we did not pursue an arm of the study in which L-NMMA was administered without phentolamine.

To confirm effective systemic α-adrenergic blockade, subjects performed two cold pressor tests (hand immersion in ice water for 3 min) before (20 min before the baseline measurements) and at the end of the protocol (2 min after the cessation of systemic α-adrenergic and NOS blockade), as illustrated in Fig. 1. Before and 2 min after the start of the hand submersion, responses of heart rate, blood pressure, cardiac output, and total vascular conductance were measured with Portapres (model 2 and BeatScope 1.0, TNO TPD Biomedical Instruments).

**Femoral artery blood flow.** Femoral artery blood flow was measured with an ultrasound machine (Sonosite 180II, Sonosite, Bothell, WA) equipped with a high-resolution multifrequency linear-array transducer as previously described (32). Briefly, the longitudinal two-dimensional and Doppler ultrasound images were consecutively obtained below the inguinal ligament, ~2–3 cm above the bifurcation into the profundus and superficial branches. Mean blood flow velocity measurements were performed with the insonation angle <60° and were corrected for insonation angle. ECG was simultaneously recorded. These images were recorded on a digital videotape for later off-line analysis. To eliminate the interinvestigator variability, the same researcher analyzed ultrasound images with computerized image-analysis software. Arterial diameter was determined by a perpendicular measurement from the media/adventitia interface of the near wall to the lumen/intima interface of the far wall of the vessel. A mean diameter was calculated based on the relative time periods of the systolic (1/3) and diastolic (2/3) blood pressure phases and was used to represent the cross-sectional area. Three measurements of arterial lumen diameter were taken per frame and averaged. Blood flow was calculated as: (mean blood velocity) \times (circumference area) \times 6 \times 10^4 (with the constant 6 \times 10^4 being the conversion factor from m/s to l/min). Data reported are the time averages of ≥10 measurements for all variables. Femoral vascular conductance was calculated as femoral artery blood flow per ankle mean artery blood pressure (15). In our laboratory, the day-to-day reproducibility of the measurements for the femoral artery diameter and blood flow were ± 1 and ± 2%, respectively.

**Cardiac output and total vascular conductance.** Cardiac output was calculated from the blood pressure waveform using the model flow method, incorporating age, sex, height, and weight (Portapres model 2 and BeatScope 1.0, TNO TPD Biomedical Instruments). We have previously demonstrated that this method provides a reliable estimation of “relative” or percent changes in cardiac output (35). Total vascular conductance was calculated as cardiac output per mean arterial blood pressure.

**Arterial blood pressure and ankle-brachial index.** Brachial and ankle arterial blood pressure and ankle-brachial index were also measured with the automated device (VP-2000, Colin Medical Instrument, San Antonio, TX) (3). An automatic oscillometric blood pressure device was used to eliminate potential investigator bias associated with auscultation.

**Body composition.** Serial cross-sectional images of the thigh on the right side were obtained by a 1.0-T MRI system (Magnetom Impact, Siemens). Gradient echo, consecutive axial-plane images (TR: 25.8 ms; TE: 9.0 ms; flip angle: 40.0 degree; slice thickness: 10 mm; inter-slice gap: 0 mm) were taken from spina iliaca anterior superior to extremitas distalis of tibia in the supine position with the subject's legs extended and relaxed. The anatomical muscle cross-sectional area (CSA) was calculated from each MR image by an Image software package (Image J 1.36b, National Institutes of Health). The baseline thigh (extensor and flexor) muscle CSA was reported by the mean CSA obtained from 11 images, i.e., the widest CSA image and each 5 image above and below it. Percent body fat was determined by...
bioelectric impedance (HBF-357, Omron Healthcare) as previously described (20).

**Blood samples.** A blood sample was collected from the antecubital vein using venipuncture after an overnight fast. Plasma concentrations of glucose, lipids, and lipoproteins were determined by use of a standard enzymatic technique as previously described (38). Plasma norepinephrine concentration was measured by high-performance liquid chromatography methods (14). Plasma samples from each subject before and after the training intervention were assayed in the same assay run.

**Aerobic capacity.** All subjects underwent an incremental cycle exercise test (after 2 min at 20 W, with 15 W increases every 1 min) until they reached 85% of the age-predicted maximal heart rate (208 − age × 0.7) (39). Heart rate (via ECG) was measured throughout the protocol. Work rate corresponding to 85% of the age-predicted maximal heart rate (PWC85%) was used as a measure of aerobic capacity. PWC85% has been shown to correlate well with directly measured maximal oxygen consumption (22).

**Aerobic exercise training intervention.** Subjects underwent aerobic training 4–5 days per week (walk/jog, 2 supervised and additional home-based trainings) for 12 wk. The duration and intensity of the training were 30–45 min/day and 65–75% of their individual maximum heart rate. Adherence to the exercise prescription was documented through the use of Polar heart rate monitors and physical activity logs. The averaged heart rate during the training was 70 ± 1% of their individual maximal heart rate. The averaged frequency and duration of the exercise training were 4.4 ± 0.1 days/wk and 44 ± 2 min/day, respectively.

**Statistical Analyses**

ANOVA and MANOVA with repeated measures were used to determine the effects of exercise training intervention, as well as the impacts of systemic α-adrenergic and NOS blockades on femoral artery hemodynamics. Changes in femoral vascular conductance from baseline to the phentolamine administration were used as indexes of "sympathetic vascular tone" as previously described by Halliwill et al. (13). Changes in femoral vascular conductance from the phentolamine administration to the combined phentolamine and L-NMMA administration were used as indexes of "NO vascular tone" (13). Sample size calculations indicated that we had 77–88% to detect statistically significant differences in femoral vascular conductance (assuming α = 0.05) in the present study. All data are reported as means ± SE. Statistical significance was set a priori at P < 0.05.

**RESULTS**

There were no significant changes in body mass, adiposity, plasma concentrations of cholesterol and glucose, or heart rate and blood pressure at rest with the exercise training intervention. Plasma norepinephrine concentration at rest and PWC85% increased significantly after the exercise training intervention (Table 1). Femoral muscle CSA increased slightly but significantly after the exercise training. Femoral artery mean diameter, blood flow at rest, and femoral artery blood flow/muscle CSA were not affected by the exercise training intervention.

Before the exercise intervention, mean arterial pressure decreased after phentolamine infusion (P < 0.05) but increased after the combined administrations of phentolamine and L-NMMA (P < 0.05) (Table 2). Accordingly, α-adrenergic blockade increased heart rate (P < 0.05) and the subsequent addition of NOS blockade reduced heart rate (P < 0.05). Mean arterial pressure responses were not different before and after the exercise intervention. Diastolic blood pressure achieved with α-adrenergic blockade was slightly but significantly lower after the exercise intervention than that before the exercise intervention. Under the combined α-adrenergic and NOS blockades, heart rate was lower after the exercise intervention than before the exercise intervention (P < 0.05).

As shown in Fig. 2, basal (resting) level of femoral artery blood flow did not change with exercise training (354 ± 29 to 335 ± 34 ml/min). Even when femoral blood flow was adjusted for thigh muscle CSA, they were not different before and after exercise training (3.2 ± 0.3 to 3.0 ± 0.3 units).

Before the training intervention, femoral artery blood flow increased 32% with α-adrenergic blockade (P < 0.05), and the addition of NOS blockade did not affect femoral artery blood flow (not significant). After the training intervention, femoral artery blood flow increased 47% with α-adrenergic blockade (P < 0.01) and then decreased 18% with L-NMMA administration (P < 0.05). Femoral blood flow and vascular conductance after the combined α-adrenergic and NOS blockades were not significantly different from the baseline values.

Basal level of femoral vascular conductance did not change with exercise training (3.6 ± 0.3 to 3.5 ± 0.3 units, Fig. 2). Before the training intervention, femoral vascular conductance increased 50% with α-adrenergic blockade (P < 0.01) and then decreased 15% with the combined α-adrenergic and NOS blockades (P < 0.05) before the training. Similarly, femoral vascular conductance increased 86% with α-adrenergic blockade (P < 0.001) and then decreased 38% with the combined α-adrenergic and NOS blockades (P < 0.001) after the training intervention. Femoral vascular conductance had a significantly greater increase in response to phentolamine after the training intervention (1.7 ± 0.5 to 3.0 ± 0.5 units, Fig. 3), suggesting the enhanced "sympathetic vascular tone" with the exercise training. Likewise, the decrease in femoral vascular conductance with the combined phentolamine and L-NMMA administrations (the index of "NO vascular tone") was augmented significantly after the training intervention (0.8 ± 0.4 to 2.7 ± 0.7 units, Fig. 4).

The cold pressor test induced significant changes in mean arterial blood pressure (before training: +25 ± 5 mmHg; after training: +17 ± 4 mmHg) and total vascular conduc-

**Table 1. Selected subject characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Before Training</th>
<th>After Training</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>60 ± 3</td>
<td>65 ± 4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161 ± 2</td>
<td>162 ± 2</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>59 ± 3.8</td>
<td>60.2 ± 3.8</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>22.9 ± 1.2</td>
<td>23.1 ± 1.2</td>
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<tr>
<td>Fat mass, %</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
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<tr>
<td>Femoral muscle CSA, cm²</td>
<td>111 ± 10</td>
<td>115 ± 11*</td>
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<tr>
<td>Heart rate at rest, beats/min</td>
<td>59 ± 4</td>
<td>57 ± 4</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>123 ± 6</td>
<td>122 ± 6</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>73 ± 3</td>
<td>71 ± 4</td>
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<tr>
<td>Femoral artery diameter, mm</td>
<td>7.8 ± 0.5</td>
<td>8.1 ± 0.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.8 ± 0.3</td>
<td>5.4 ± 0.2</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.6 ± 0.1</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>3.6 ± 0.2</td>
<td>3.2 ± 0.2</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.3</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>5.2 ± 0.1</td>
<td>5.4 ± 0.2</td>
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<td>Plasma norepinephrine, pg/ml</td>
<td>210 ± 35</td>
<td>330 ± 32*</td>
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<tr>
<td>PWC85%, watt</td>
<td>104 ± 11</td>
<td>114 ± 11*</td>
</tr>
</tbody>
</table>

Data are means ± SE. CSA, cross-sectional area; BP, blood pressure; PWC85%, physical work capacity corresponding to 85% of the age-predicted maximal heart rate. *P < 0.05 vs. baseline.
Table 2. Hemodynamic measures in response to α-adrenergic and NOS blockade before and after exercise training

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>α-Adrenergic Blockade</th>
<th>Combined α-Adrenergic and NOS Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>Before</td>
<td>59 ± 4</td>
<td>70 ± 5†</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>57 ± 4</td>
<td>71 ± 5†</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>Before</td>
<td>124 ± 6</td>
<td>109 ± 5†</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>121 ± 6</td>
<td>103 ± 6†</td>
</tr>
<tr>
<td>Mean arterial BP, mmHg</td>
<td>Before</td>
<td>94 ± 6</td>
<td>79 ± 5†</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>93 ± 4</td>
<td>76 ± 4†</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>Before</td>
<td>72 ± 3</td>
<td>65 ± 3†</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>70 ± 4</td>
<td>59 ± 4†</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>Before</td>
<td>52 ± 4</td>
<td>44 ± 3</td>
</tr>
<tr>
<td></td>
<td>After</td>
<td>50 ± 4</td>
<td>47 ± 3</td>
</tr>
</tbody>
</table>

Data are means ± SE. BP, blood pressure; NOS, nitric oxide synthase.

*P < 0.05 vs. before training; †P < 0.05 vs. baseline; ‡P < 0.05 vs. α-adrenergic blockade.

Discussion

The salient findings of the present study are as follows. First, basal femoral blood flow remained unchanged with exercise training in previously sedentary older adults. Second, local and systemic NO vascular tone, as determined by hemodynamic changes with NOS blockade, increased after endurance training. Finally, endurance training increased local and systemic sympathetic vascular tone as reflected by greater increases in femoral vascular conductance with α-adrenergic blockade after exercise training. These results suggest that the increases in sympathetic vasoconstrictor tone on the vasculature are necessary to offset the training-induced enhancement of NO bioavailability to maintain basal limb blood flow and vascular conductance with endurance training.

Endurance-trained state is associated with an elevated level of muscle sympathetic nervous system activity at rest, at least in middle-aged and older adults (24, 26). Additionally, a short-term endurance training increases plasma norepinephrine concentrations as well as norepinephrine spillover rates in healthy older adults (26). We found that after the exercise training intervention, greater increases were observed in femoral artery blood flow and vascular conductance in response to phentolamine infusion suggesting that local and systemic sympathetic vascular tone increased with endurance training. This was associated with significantly higher resting plasma norepinephrine concentration after endurance training. Thus the present findings are consistent with the majority of findings suggesting that regular aerobic exercise training is associated with augmented basal sympathetic nervous system activity in healthy middle-aged and older adults (24, 26). Interestingly, the augmented α-adrenergic vasoconstrictor tone after endurance training was not associated with a reduction in basal leg blood flow in the present study.

Endothelium-dependent vasodilation and NO bioavailability diminish with advancing age (4, 36, 37). On the other hand, accumulating evidence indicates that regular aerobic exercise training is associated with reversal of, at least some portion of, the age-related decline in endothelial function in humans (4, 17, 36). In a cross-sectional study, Taddei and colleagues (36) documented that NOS inhibitor-induced vasoconstriction was greater in well-trained older subjects than in age-matched sedentary controls. Using indirect measures of NO bioavailability, we have also demonstrated that 3 mo of moderate aerobic exercise training increases resting plasma concentrations of NOx and cGMP in sedentary older women (17). In the present intervention study using a pharmacological approach, we found a significantly greater decrease in femoral vascular conductance with L-NMMA administration after the training intervention. Taken together, these results are consistent with the hypothesis that aerobic exercise training increases NO bioavailability/release in middle-aged and older sedentary adults.
It is possible to hypothesize that the greater sympathetic vasoconstrictor tone induced by aerobic exercise training may be necessary to offset the concomitantly enhanced NO bioavailability to maintain basal limb blood flow and vascular conductance. There are several experimental observations in the literature to support the interaction between sympathetic nervous system activity and NO. As demonstrated in an isolated blood vessel preparation, NO is capable of acting directly on vascular smooth muscle to attenuate sympathetic vasoconstrictor tone (41). Moreover, release of norepinephrine from postganglionic sympathetic nerve endings is modulated by NO (12). A recent study (9) demonstrated that aging augments β-adrenergic vasoconstriction while exercise training attenuates this response, and both of these alterations are mediated through an endothelial receptor-NOS-signaling pathway. Furthermore, studies dealing with the “functional sympatholysis,” a phenomenon characterized by a blunted vasoconstrictor response to sympathetic activation in exercising muscles, substantiated a role of NO in modulating sympathetic neural control of muscle blood flow (2, 40) although this question still remains controversial especially in humans (6). Our results extend these observations in acute exercise settings to chronic exercise training by suggesting that the interactive effects of sympathetic nervous system and NO on limb blood flow observed during an acute exercise session may also be operative in the chronic adaptations of limb blood flow to endurance training.

Fig. 3. Effect of endurance training on “sympathetic vascular tone.” Changes in femoral BF and vascular conductance from the baseline to the phentolamine administration were used as an index of local and systemic sympathetic vascular tone.

Fig. 4. Effect of endurance training on “nitric oxide vascular tone.” Changes in femoral BF and vascular conductance from the phentolamine administration to the combined phentolamine and L-NMMA administration were used as an index of local and systemic NO vascular tone.

Basal limb blood flow decreases with advancing age even in healthy humans (5, 7, 23). Reduced peripheral blood flow has been suggested to be mechanistically involved in the metabolic syndrome, a cluster of disease states that include hyperinsulinemia, dyslipidemia, and hypertension (16). We found that basal limb blood flow did not change with 3 mo of regular aerobic exercise in older adults. Our present finding is consistent with previous cross-sectional and interventional studies showing a lack of influence of regular aerobic exercise on basal conduit artery blood flow (7, 19). Recently, a study involving young adults has demonstrated that changes in limb blood flow induced by insulin modulate protein synthesis in skeletal muscle (11). As insulin evokes vasodilatation via NO mechanisms and insulin-induced vasodilatory capacity is known to decrease with advancing age (10), reduced levels of basal limb blood flow may be mechanistically linked with the pathogenesis of sarcopenia, the age-associated loss of muscle mass and function. In this context, it is interesting to note that endurance training does not appear to modulate the age-associated loss of appendicular muscle mass (34) as it does not affect basal limb blood flow. On the other hand, we have recently demonstrated that habitual resistance training, which evokes increases in muscle mass, exerts a significant effect on basal limb blood flow in aging humans (1, 21).

Several limitations in this study should be noted and emphasized. First, systemic infusion of NOS inhibitors would induce sustained increases in arterial pressure, which would be a potent stimulus to activate arterial baroreceptors resulting in a reflex suppression of sympathetic nervous system activity. As such, we cannot exclude the possibility that systemic hemodynamic changes may have influenced our findings focusing on local (leg) circulation. However, relative changes in cardiac output during pharmacological interventions were similar before and after exercise training. Second, vasodilatory capacity during submaximal exercise is preserved in aged men (27) but appears to be impaired in aged women (28). Additionally, the age-related decline in basal limb blood flow is strongly mod-
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ulated by sympathetic vasoconstrictor tone in men (5), whereas no such association seems to exist in women (23). Considering that we have included both sexes in this study, these are important considerations. However, these sex-related effects seem to be mediated through the modulatory influence of estrogen on locally produced vasoactive factors such as NO, and we studied only postmenopausal (i.e., estrogen deficient) women who did not take hormone replacement therapy. Additionally, there were no appreciable differences in responses to pharmacological interventions or exercise training between men and women. Moreover, in the context of the present study, both men and women experience similar age-related reductions in basal limb blood flow (5, 7, 23), and there is no association between endurance training and basal limb blood flow in both men and women (7). Finally, there was no sedentary or younger control group included in the present study. As such, we have no data to demonstrate that the observations that we made are operating exclusively in middle-aged and older adults.

In summary, the aim of the present study was to determine the effects of endurance training on basal femoral blood flow, α-adrenergic vasoconstriction, and NO bioavailability in older healthy adults. We found that endurance training did not change basal limb blood flow but enhanced endothelium function as well as sympathetic nervous system activity. Our present results suggest that basal limb blood flow does not change with endurance training and that this is associated with competing effects of heightened sympathetic nervous system activity and enhanced NO bioavailability on the vasculature.

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