Role of $\alpha_1$-adrenergic vasoconstriction in the regulation of skeletal muscle blood flow with advancing age

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1Department of Medicine, University of California, San Diego, La Jolla, California; 2Department of Internal Medicine, Division of Geriatrics, and 3Department of Exercise and Sport Science, University of Utah, and 4Geriatric Research and Clinical Center, Salt Lake City Veterans Affairs Medical Center, Salt Lake City, Utah

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Wray DW, Nishiyama SK, Richardson RS. Role of $\alpha_1$-adrenergic vasoconstriction in the regulation of skeletal muscle blood flow with advancing age. *Am J Physiol Heart Circ Physiol* 296: H497–H504, 2009. First published December 5, 2008; doi:10.1152/ajpheart.01016.2008.—$\alpha_1$-Adrenergic vasoconstriction during dynamic leg exercise is diminished in younger individuals, although the extent of this exercise-induced “sympatholysis” in the elderly remains uncertain. Thus, in nine young ($25 \pm 1$ yr) and six older ($72 \pm 2$ yr) healthy volunteers, we evaluated changes in leg blood flow (ultrasound Doppler) during blood-flow-adjusted intra-arterial infusion of phenylephrine (PE; a selective $\alpha_1$-adrenergic agonist) at rest and during knee-extensor leg exercise at 20, 40, and 60% of maximal work rate (WRmax). To probe the potential contributors to exercise-induced changes in $\alpha_1$-adrenergic receptor sensitivity, exercising leg O2 consumption ($\dot{V}$O2) and lactate efflux were also evaluated ($n=10$). At rest, the PE-induced vasoconstriction (i.e., decrease in leg blood flow) was diminished in older ($–37 \pm 3\%$) compared with young ($–54 \pm 4\%$) subjects. During exercise, the magnitude of $\alpha_1$-adrenergic vasoconstriction in the active leg decreased in both groups. However, compared with young, older subjects maintained a greater vasoconstrictor response to PE at 40% WRmax ($–14 \pm 3\%$, older; $–7 \pm 2\%$, young) and 60% WRmax ($–11 \pm 3\%$, older; $–4 \pm 3\%$, young). It is possible that this observation may be attributed to lower absolute work rates in the older group, because, for a similar absolute work rate ($\approx 10$ W) and leg $\dot{V}$O2 ($\approx 0.36$ l/min), vasoconstriction to PE was not different between groups ($–14 \pm 3\%$; older; $–17 \pm 5\%$, young). Together, these data challenge the concept of reduced sympatholysis in the elderly, suggesting instead that the inhibition of $\alpha_1$-adrenergic vasoconstriction in the exercising leg is associated with work performed and, therefore, more closely related to the rate of oxidative metabolism than to age per se.

AGING IS ASSOCIATED WITH A variety of adaptations within the vascular system that collectively contribute to a decline in the capacity to regulate skeletal muscle blood flow. Chief among these changes is an elevation in tonic sympathetic nerve activity (4, 20, 37), which is thought to result in a desensitization of end-organ (i.e., $\alpha$-adrenergic) receptor sensitivity. Indeed, recent studies in both the forearm (7) and leg (36) have identified an age-related decline in vasoconstriction following sympathomimetic drug infusion at rest, a diminution that may be due to $\alpha$-adrenergic receptor downregulation, desensitization, or a general decline in signal transduction attributable to vascular aging. Somewhat paradoxically, resting limb blood flow is typically reduced in the elderly, despite this decline in $\alpha$-adrenergic responsiveness.

Much less is known about $\alpha$-adrenergic regulation during physical activity in older individuals. However, our group (15, 26) and others (27, 28) have documented a reduction in exercising limb blood flow in the elderly, an event that may potentially result in an inequality between tissue perfusion and metabolic demand in the active muscle tissue, ultimately compromising the ability to perform physical activity. There is some evidence that this age-related reduction in blood flow during exercise could be related to $\alpha$-adrenergic receptor sensitivity within the vasculature of the active limb. Indeed, in the young, $\alpha$-adrenergic vasoconstriction is blunted during leg exercise in an intensity-dependent manner (3, 44), a phenomenon originally called “functional sympatholysis” (30). In an effort to examine this process in the elderly, Dineno et al. (6) recently demonstrated that vasoconstriction in response to intra-arterial phenylephrine (PE; a selective $\alpha_1$-agonist) and tyramine (evokes endogenous norepinephrine release) was maintained to a greater extent during handgrip exercise in older subjects. Additionally, using the cold pressor test (CPT) to evoke systemic sympathoexcitation, Koch et al. (13) identified a blunted vasoconstriction in the elderly compared with young during cycle exercise. Furthermore, in a study of pre- and postmenopausal women, Fadel et al. (9) demonstrated an age-related decline in arm vasoconstriction during sympathoexcitation evoked by orthostatic stress (lower body negative pressure). Together, these studies have provided some evidence of a sustained capacity for $\alpha$-adrenergic vasoconstriction during exercise with age, findings that have promoted the concept of “impaired sympatholysis” in the elderly.

To our knowledge, specific changes in $\alpha_1$-adrenergic vasoconstriction in the exercising leg vasculature of the elderly, and whether the pattern of this response differs as a consequence of exercise intensity, have not been characterized. Thus the present study sought to determine the effect of age on $\alpha_1$-adrenergic vasoconstriction in the leg at rest and during exercise. Changes in leg blood flow (LBF) and vascular conductance were evaluated during intra-arterial administration of PE at rest and during three levels of knee-extensor (KE) exercise, with the drug dose adjusted according to LBF. We hypothesized that 1) older individuals would exhibit a reduced sensitivity to PE at rest compared with young; and 2) KE exercise would blunt PE-mediated vasoconstriction in both groups, but to a greater extent in the young than their older counterparts.

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METHODS

Nine young (25 ± 1 yr, n = 8 men, n = 1 woman) and six older (72 ± 2 yr, n = 6 men) healthy subjects were enrolled in the present study. All subjects were nonsmokers, normotensive (<140/90 mmHg), and were normally active but not enrolled in any regular exercise program. Subjects were not taking any prescription medication and were free of overt cardiovascular disease, as indicated by physical exam and 12-lead cardiac stress testing. Protocol approval and informed consent were obtained according to the University of California San Diego Human Subjects Protection Program requirements. Subjects reported to the laboratory on a preliminary day to complete health histories and physical examinations and perform a graded single-leg KE test to determine maximal work rate (WRmax).

Experimental Protocols

Day 1. Subjects reported to the laboratory at 0800 on the experimental day. An arterial catheter was placed proximally in the common femoral artery (CFA) using sterile technique, as previously reported (2, 46). After catheter placement, subjects rested for ~30 min and then underwent the protocol as outlined in Fig. 1. All data collection took place with subjects in a semirecumbent position (~60° reclined), and all studies were performed in a thermoneutral environment.

PE (Sigma-Aldrich, St. Louis, MO) was administered as a selective α1-adrenergic agonist. PE was prepared at a concentration of 2.5 µg/ml of 0.9% sterile saline and infused intra-arterially for 2.5 min at a blood flow-adjusted rate of 8.3 ng/ml LBF (0.5–15 ml/min) using a constant-speed infusion pump (Harvard Apparatus, Holliston, MA). Immediately before infusion, real-time blood flow was determined using the ultrasound Doppler, and infusion rate was blood flow adjusted according to these “on-the-fly” blood flow values to ensure similar effective concentration of the drug at rest and during exercise. Our laboratory has previously identified the dose-response relationship of PE in the human leg (44) and, for the present study, selected a dose that would elicit significant vasoconstriction but limit the risk of systemic spillover during the higher infusion rates that occurred during KE exercise.

The nonspecific β-adrenergic antagonist propranolol (Sigma-Aldrich) was prepared at a concentration of 10 µg/ml of 0.9% sterile saline and added to the PE infusate to block potential β2-mediated vasodilation during PE infusion (40).

Day 2. In an effort to examine the mechanisms responsible for the observed responses to PE, 10 subjects (n = 6 younger, n = 4 older) who participated on day 1 returned to the laboratory within 2 wk to perform KE exercise (described below) following both arterial and venous catheterization. Arterial and venous blood samples (2–3 ml) for blood-gas and lactate analyses were collected at rest and during a graded exercise protocol identical to that performed on experimental day 1 (Fig. 1).

Exercise model. The KE paradigm implemented in this study has been described previously. Briefly, subjects were seated on an adjustable chair, with a cycle ergometer (model 828e, Monark Exercise, Vansbro, Sweden) placed behind them. Resistance was provided by friction on the flywheel, which was turned by the subject via a metal bar connected to the crank of the ergometer and a boot attached to the ankle of the subject. Sixty contractions per minute were maintained at each work rate. Subjects exercised at 20, 40, and 60% of their WRmax, determined on the preliminary visit (Fig. 1).

Measurements

LBF was evaluated using an ultrasound Doppler system (Logiq 7, GE Medical Systems, Milwaukee, WI) equipped with a linear array transducer, operating at an imaging frequency of 10 MHz. The CFA was insonated 2–3 cm proximal to the bifurcation of the CFA into the superficial and deep branches, distal to the tip of the femoral catheter. The blood velocity profile was obtained using the same transducer with a Doppler frequency of 4.0–5.0 MHz, operated in the high-pulsed repetition frequency mode (2–25 kHz), and the sample volume was placed at a depth of 1.5–3.5 cm. Aliasing was prevented using scale adjustments, especially during exercise. All blood velocity measurements were obtained with the probe appropriately positioned to maintain an insolation angle of 60°. The sample volume was maximized according to vessel size and centered, verified by real-time ultrasound visualization of the vessel. At all sample points, arterial diameter and angle-corrected, intensity-weighted mean blood velocity (Vmean) values were calculated using commercially available software (Logiq 7, GE Medical Systems, Milwaukee, WI). Using measured artery diameter and Vmean, blood flow was calculated as follows: blood flow (ml/min) = Vmean × π × (vessel diameter)²/4.

The “magnitude of sympatholysis” was determined by comparing PE-induced changes in LBF at rest to those observed during exercise, reflecting the ability of muscle contractions to blunt PE-induced vasoconstriction during exercise (6, 43). This index was calculated as follows: magnitude of sympatholysis (%) = PE-induced change in LBF at rest (%) − PE-induced change in LBF during exercise (%).

Arterial blood pressure measurements were collected continually from within the femoral artery, with the pressure transducer placed at the level of the catheter (Transpac IV, Abbot Laboratories). Mean arterial pressure (MAP; mmHg) was calculated using the time integral of the arterial waveform (sampled at 150 Hz). Leg vascular conductance (LVC; ml·min⁻¹·mmHg⁻¹) was calculated as follows: LBF/MAP. Heart rate (HR) was monitored from a standard three-lead ECG as an integral part of the Doppler system (Logiq 7, GE Medical Systems, Milwaukee, WI).

Samples of arterial and venous blood were presented anerobically to an IL synthesis blood-gas analyzer and IL 682 cooximeter (Clayton, NC). Blood O2 content (CðO2Þ) was calculated as 1.39 (Hb) × (SO2/100) + 0.003 × P02, where SO2 is oxyhemoglobin saturation. O2 extraction was calculated as the difference between the femoral artery CðO2Þ(CaO2) and femoral venous CðO2Þ(CvO2) divided by CaO2, [× 100 (%)]. O2 delivery was calculated as the product of LBF and CaO2, and muscle O2 consumption (VO2) as the product of CaO2−CvO2 difference and LBF. Whole blood lactate was assayed enzymatically using a semiautomated analyzer (1500, Yellow Springs Instruments, Yellow Springs, OH). Net venous lactate outflow was calculated according to the Fick principle by multiplying LBF by the venoarterial lactate concentration difference.

![Fig. 1. Experimental timeline. Arrows indicate time intervals for leg blood flow measurements. PRE, preinfusion; PE, phenylephrine; KE, knee-extensor exercise; WRmax, maximal KE work rate.](http://ajpheart.physiology.org/)

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Data Analysis and Statistics

Ultrasound images and Doppler velocity waveforms were recorded continuously, with serial 45-s segments recorded before and during drug infusions. For each 45-s ultrasound Doppler segment, $V_{mean}$ was averaged across three 15-s intervals, with intima-to-intima diameter measurements evaluated during diastole, as described previously (8, 48).

Due to the anticipated decline in maximal KE exercise capacity in older subjects, we initially assessed our measurements at similar relative exercise intensities. However, because inhibition of $\alpha$-adrenergic vasoconstriction appears to vary according to absolute exercise intensity (3, 44), post hoc analysis of responses using a single absolute work rate of 10 W was also performed to evaluate potential age-related differences at comparable levels of leg Vo$_2$.

Statistics were performed with the use of commercially available software (SigmaStat 3.10, Systat Software, Point Richmond, CA). Repeated-measure analysis of variance, analysis of variance, and Student $t$-tests were used to identify significant changes in measured variables within and between drug groups and across exercise intensities, with the Bonferroni test used for post hoc analysis when a significant main effect was found. All group data are expressed as means $\pm$ SE. Significance was established at $P < 0.05$.

RESULTS

Subject characteristics are presented in Table 1.

**PE at Rest**

In both young and old groups, administration of the $\alpha_1$-adrenergic agonist PE (8.3 ng ml$^{-1}$ min$^{-1}$) did not significantly change HR or MAP after 2.5 min of continuous infusion (Table 2). However, this intra-arterial infusion did provoke a significant and marked local reduction in CFA diameter, LVC, and LBF (Table 2, Fig. 2). Compared with young, the older group exhibited significantly smaller changes in CFA diameter ($-24 \pm 4\%$ young vs. $-6 \pm 3\%$ older), LBF ($-54 \pm 4\%$ young vs. $-37 \pm 3\%$ older), and LVC ($-55 \pm 5\%$ young vs. $-36 \pm 5\%$ older) at the end of the PE infusion (Table 2, Figs. 2 and 3).

**PE During Exercise**

During exercise, the infusion rate of PE was adjusted to match the increase in blood flow in both young ($15 \pm 1$, $17 \pm 2$, and $20 \pm 2$ $\mu$g min$^{-1}$ at 20, 40, and 60% WR$_{max}$, respectively) and older ($16 \pm 4$, $23 \pm 1$, and $26 \pm 2$ $\mu$g min$^{-1}$ at 20, 40, and 60% WR$_{max}$, respectively) groups. Despite this increase in dose, no significant changes in HR or MAP were observed after PE infusion (Table 2). PE significantly decreased CFA diameter, LBF, and LVC at lower exercise intensities, with blunted effects during the higher intensities (Table 2, Figs. 2 and 3). At 40 and 60% WR$_{max}$, older subjects maintained a significantly greater vasoconstriction in response to PE com-

Table 1. Subject characteristics

<table>
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<th>Young</th>
<th>Older</th>
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<tr>
<td>Age, yr</td>
<td>25±1</td>
<td>72±2*</td>
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<tr>
<td>Height, cm</td>
<td>159±10</td>
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<tr>
<td>Weight, kg</td>
<td>67±1</td>
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<td>Body mass index, %</td>
<td>23±1</td>
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<td>Quadriceps muscle mass, kg</td>
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<td>Maximal knee-extensor work rate, W</td>
<td>50±5</td>
<td>28±5*</td>
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Values are means ± SE. *Significantly different from young group, $P < 0.05$.

Table 2. Cardiovascular measurements at rest and during exercise

<table>
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<td>61±4</td>
<td>69±1*</td>
<td>74±1</td>
<td>49±1*</td>
<td>69±1*</td>
<td>55±8</td>
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<td>115±3</td>
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<td>83±1*</td>
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<td>77±1*</td>
<td>83±1*</td>
<td>77±1*</td>
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<td>83±1*</td>
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<tr>
<td>MAP, mmHg</td>
<td>115±3</td>
<td>121±5*</td>
<td>127±5</td>
<td>122±1*</td>
<td>121±5*</td>
<td>122±1*</td>
<td>127±5</td>
<td>122±1*</td>
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<tr>
<td><strong>40% WR$_{max}$</strong></td>
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<td>HR, beats/min</td>
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<td>90±1</td>
<td>97±1*</td>
<td>83±1*</td>
<td>90±1</td>
<td>83±1*</td>
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<td>90±1</td>
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<td>MAP, mmHg</td>
<td>122±4</td>
<td>129±2*</td>
<td>131±2</td>
<td>122±2*</td>
<td>129±2*</td>
<td>122±2*</td>
<td>131±2</td>
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<td><strong>60% WR$_{max}$</strong></td>
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<tr>
<td>HR, beats/min</td>
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<td>94±1*</td>
<td>101±2</td>
<td>87±2</td>
<td>94±1*</td>
<td>87±2</td>
<td>101±2</td>
<td>94±1*</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>126±5</td>
<td>133±3*</td>
<td>139±3</td>
<td>126±3*</td>
<td>133±3*</td>
<td>126±3*</td>
<td>139±3</td>
<td>133±3*</td>
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</table>

*Significantly different than young group, $P < 0.05$.
pared with young across relative work rates (Fig. 2, A and B). The “magnitude of sympatholysis”, i.e., the difference in PE-induced vasoconstriction between rest and exercise, was significantly different between groups at each relative or at a single absolute (10-W) work rate, with the young exhibiting a greater sympatholysis. (Fig. 2 C). However, because this calculation may be biased by resting responses that may not be present during exercise, PE-induced changes in LBF were also viewed according to absolute work rate (Fig. 4, top). When the data are expressed in this way, a significant relationship was observed ($R = 0.635, P < 0.001$), with a similar slope (65 ± 10 young vs. 55 ± 6 old) and y-intercept ($-38 ± 6$ young vs. $-35 ± 4$ older) between groups.

**Arteriovenous Blood Samples**

Metabolic measurements at rest and during exercise are presented in Table 3. At rest, arterial and venous blood sample analysis revealed no age-related difference in $V_{O2}$, arterial lactate, and venous lactate. However, maximal KE work rates were significantly lower in the older group (28 ± 5 W) compared with young (50 ± 5 W). Thus, during exercise at three relative intensities, leg $V_{O2}$ was 20–40% lower in older compared with young, but was accompanied by higher lactate efflux (20 and 40% WRmax). As expected, when groups were compared at a single absolute work rate (10 ± 1 W), leg $V_{O2}$ was not different between young and older subjects, although lactate efflux was elevated in the older group at this exercise intensity (Table 3, Fig. 4).

**DISCUSSION**

The present study has both confirmed prior findings and questioned developing concepts concerning the role of $\alpha_1$-adrenergic vasoconstriction with advancing age. At rest, intra-arterial infusion of the selective $\alpha_1$-agonist PE in the human leg demonstrated an age-related decline in $\alpha_1$-adrenergic receptor sensitivity, substantiating earlier findings in the elderly (36). During KE exercise, PE-induced vasoconstriction was reduced in both young and old, indicating a blunted postjunctional $\alpha_1$-adrenergic responsiveness in the vasculature of the active muscle tissue. When groups were compared at the same relative exercise intensities (20, 40, and 60% WRmax), an apparent preservation of $\alpha$-adrenergic responsiveness was observed in the elderly. It is possible that this finding may be attributed to lower absolute work rates at each exercise intensity in the older group. Indeed, when the same age comparison was made at an absolute exercise intensity where leg $V_{O2}$ was similar between groups, no age-related difference in PE-induced vasoconstriction was evident. Taken together, these data raise some doubts concerning an age-related decline in sympatholysis, with the implication that inhibition of $\alpha_1$-adrenergic vasoconstriction in...
was blunted in older compared with young subjects. This diminution in responsiveness of $\alpha_1$-receptors in the elderly group may be the consequence of an age-related elevation in muscle sympathetic nerve activity (35), since these receptors serve as the end-organ component of this autonomic regulatory pathway. However, it remains unknown whether this age-related decline in $\alpha_1$-mediated vasoconstriction is related to a decline in receptor sensitivity, density, or changes in receptor distribution. The present findings at rest confirm recent work by Smith et al. (36), who reported blunted responses to PE during a similar experimental paradigm.

Previously, nonselective $\alpha$-adrenergic antagonist administration (phentolamine) in an elderly cohort improved an age-related decline in resting LVC, such that it was concluded $\alpha$-adrenergic vasoconstriction may account for $\sim$75% of the age-related elevation in vascular tone (7). Although this prior work provides convincing evidence that the sympathetic-adrenergic pathway is indeed a key component in the dysregulation of skeletal muscle blood flow in the elderly, it leaves open the possibility that other regulatory mechanisms, such as angiotensin II (46), endothelin-1 (39, 41), or oxidative stress (11), may also contribute to a reduction in resting limb blood flow with advancing age.

$\alpha_1$-Mediated Vasoconstriction During Exercise: Absolute vs. Relative Intensity

In agreement with previous human studies from our group (3, 44) and others (5, 6, 32), in the present study both young and old groups demonstrated some loss of $\alpha_1$-mediated vasoconstriction during KE exercise (Fig. 2). PE-induced vasoconstriction was greater at 40 and 60% of maximal exercise intensity in older subjects compared with their younger counterparts, a response that initially seemed to suggest this receptor subtype was less susceptible to exercise-induced metabolic inhibition in the leg. However, confounding these initially simple observations was the finding that maximal KE exercise capacity was significantly lower in the older group ($28 \pm 5 \text{ W}$) compared with young ($50 \pm 5 \text{ W}$), raising the issue of whether the observed differences in leg $\alpha_1$ sensitivity could be attributed to the fact that older subjects did not reach absolute work rates high enough to provoke full attenuation of this receptor group. Thus, while the a priori design of the present study was focused on a relative exercise intensity paradigm, the inclusion of multiple intensity levels offered the unique opportunity for post hoc examination of PE-mediated vasoconstriction at both relative and absolute work rates.

Table 3. Metabolic measurements at rest and during exercise

<table>
<thead>
<tr>
<th></th>
<th>Young</th>
<th>Old</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>20%</td>
</tr>
<tr>
<td>$\text{WR}_{\text{max}}$, W</td>
<td>10±1</td>
<td>19±2</td>
</tr>
<tr>
<td>Leg $\text{VO}_{2}$, l/min</td>
<td>0.03±0.01</td>
<td>0.37±0.03</td>
</tr>
<tr>
<td>$\text{aLA}$, mmol</td>
<td>0.57±0.05</td>
<td>0.72±0.07</td>
</tr>
<tr>
<td>$\text{vLA}$, mmol</td>
<td>0.69±0.04</td>
<td>0.94±0.13</td>
</tr>
<tr>
<td>LA eff, mmol/min</td>
<td>48±12</td>
<td>643±190</td>
</tr>
</tbody>
</table>

Values are means ± SE. $\text{WR}_{\text{max}}$, percentage of maximal work rate; $\text{WR}_{\text{abs}}$, absolute work rate; $\text{VO}_{2}$, $\text{O}_{2}$ consumption; $\text{aLA}$, arterial lactate concentration; $\text{vLA}$, venous lactate concentration; LA eff, lactate efflux. Values in bold emphasize the comparison between young and old at a similar absolute work rate ($\sim 10 \text{ W}$). *Significant difference between young and old at a similar relative exercise intensity, $P < 0.05$.
When young and old responses to PE are viewed according to absolute work rate, two noteworthy observations may be seen. First, at a single work rate achieved by both groups (10 W), no difference in vasoconstriction in response to similar doses of PE (16 ± 4 μg/min, young; 17 ± 2 μg/min, older) was apparent between groups (Table 2, Fig. 4). Although this work rate clearly represents a greater relative effort in the old (40% WRmax) than in the young (20% WRmax), this comparison offers the advantage of viewing α1-receptor sensitivity between groups in a condition where the leg musculature performs a similar amount of mechanical work and thus a comparable metabolic cost. This is in agreement with our laboratory’s previous findings in the exercising leg of young subjects, which reported a clear progression of postjunctional α-adrenergic inhibition during increasing levels of absolute work (3, 44). Second, a clear relationship may be seen when viewing PE-induced vasoconstriction in terms of absolute work rate (Fig. 4, top) and metabolic rate (Fig. 4, bottom) in both young and old. Indeed, linear regression analysis confirmed that mean slope and y-intercept values are almost identical between young and old groups. Together, these findings suggest that the degree of sympatholysis in the leg may be interpreted differently when viewed as absolute and relative exercise intensity, especially when comparing groups with dissimilar exercise capacities.

The present data are in contrast with recent studies examining age-related changes in sympathetic vasoconstriction during exercise. Using the CPT for systemic sympathoexcitation, Koch et al. (13) described a blunted vasoconstriction in the elderly during cycle exercise at 60% maximum VO2. However, the lack of resting CPT measurements and the use of an intervention with profound systemic effects make findings from this study somewhat nonspecific and difficult to compare to the present data. Also using a systemic sympathoexcitatory stimulus (orthostatic stress), Fadel et al. (9) identified a reduced ability of handgrip exercise to blunt arm vasoconstriction in postmenopausal women. A more recent study by Dinenny et al. (6) evaluated arm vasoconstriction in response to sympathomimetic drug administration in young and older individuals and reported that older subjects maintained a greater sensitivity to both α1- and α2-agonists during rhythmic handgrip exercise compared with high-flow control conditions. Together, these studies identified an “impaired sympatholysis” in the elderly during cycling and handgrip exercise, respectively.

One principal difference between these earlier works and the present study is related to the experimental exercise paradigm. Each of these previous studies employed only one level of exercise and thus were not designed to examine the intensity-dependent nature of the sympatholytic response. Furthermore, in the study of Koch et al. (13), subjects performed cycling exercise at a percentage of maximal effort, leaving some uncertainty as to whether older and younger subjects experienced a similar metabolic milieu during exercise in these prior studies, which is thought to contribute to the exercise-induced attenuation of α-adrenergic receptors. In agreement with interpretation of the present findings, the authors recognized that preservation of vasoconstriction in response to the CPT in the elderly may have been due to the lower absolute work rates in the older group, such that “the amount of metabolites available to interfere with sympathetic vasoconstriction may have been lower in the older men” (13). In the arm, both Fadel et al. (9) and Dinennu et al. (6) reported similar values for maximal voluntary contraction (handgrip) between young and older subjects. As such, the relative workload (30 and 15% maximal voluntary contraction, respectively) used in these studies was a similar absolute value in young and older groups, and thus the findings of impaired sympatholysis in the elderly cannot be attributed to lower workloads in these previous studies.

Nonetheless, it is unclear whether the reported impairment of vasoconstriction in the elderly during handgrip exercise is comparable to dynamic KE exercise, as the latter exercise modality utilizes a far greater range of motion and muscle mass (8). Indeed, it should be emphasized that a growing body of work from our group (8, 21–23, 47) and others (18, 19, 24, 31, 42) has identified a limb specificity in vascular function, including responses to PE (25). Thus recognition that the present study was performed in the leg is essential for interpretation of the present findings and indeed may partially explain the disparity in responses between the present study and prior work in the exercising forearm (6, 9). Clearly, systematic study of both arm and leg responses to exogenous sympathomimetics in the same individuals would serve to better define potential age-related changes in sympatholysis.

With the inclusion of multiple work rates and an absolute vs. relative work rate comparison, the present data thus build upon these former studies, suggesting that the potential impairment of α1-adrenergic vasoconstriction in the elderly may be dependent on whether exercise is viewed in relative (Fig. 2) or absolute (Fig. 3) terms, with no apparent age-related differences at similar levels of muscular work and leg VO2 (Figs. 3 and 4). Together, these findings suggest that the differences in exercise-induced inhibition of α1-adrenergic vasoconstriction between young and old may not be as pronounced as previously reported, emphasize the need for considering the metabolic challenge of exercise when comparing these groups, and present a clear need for further study to better characterize potential age-related changes in this important regulatory pathway.

Age and α1-Adrenergic Receptors in the CFA

At rest, infusion of PE provoked a much greater decrease in conduit vessel diameter in younger subjects compared with the elderly group (Fig. 3), again confirming recent findings by Smith et al. (36). This fivefold greater femoral artery vasoconstriction in young compared with old is a much greater between-group difference than might be expected, considering the more modest changes in LBF in response to PE, where only a 30% difference in LBF (Fig. 2A) and LVC (Fig. 2B) is evident between groups. Specifically, PE decreased LBF by almost 40%, with a concomitant conduit vessel vasoconstriction of only 5%, whereas young responded with 54 and 25% decreases in LBF and femoral artery diameter, respectively. Thus, while the present data do not directly address age-related differences in receptor sensitivity and density, it appears from these responses that the distribution of α1-receptors in the vasculature of the leg may differ with age. Based on the distinct pattern of conduit vessel vasoconstriction and LBF changes in response to PE, we speculate that the number of functional α1-receptors may be reduced in the CFA of the elderly, and that the predominant site of α1-adrenergic regulation is thus found in the distal resistance vasculature of the leg. This concept is supported by animal work identifying an...
age-related reduction in $\alpha_1$-receptor density in large-conduit arteries, such as the rat aorta (14, 38).

The vasoconstriction observed in the CFA was abolished during exercise in young subjects, in agreement with previous work from our group examining sympatholysis during leg exercise (3, 44, 45). While the CFA is not thought to be a functionally significant site of regulation for perfusion of the leg during exercise (29), the striking lack of conduit artery vasoconstriction following PE further demonstrates the profound, intensity-dependent effect of exercise on $\alpha_1$-receptor responsiveness in the human leg. The fact that this receptor population becomes less sensitive to exogenous PE during exercise in a region that is presumably far removed from the metabolic milieu emanating from the exercising muscle suggests a complex regulatory mechanism that involves more than exercise-induced metabolites. In the elderly, PE-induced changes in femoral artery diameter at rest were minimal, and thus changes in vasoconstriction from rest to exercise were statistically insignificant (Fig. 3), making it difficult to interpret the response of this cohort in the context of sympatholysis. Nonetheless, it is possible that the apparent age-related decline in functional $\alpha_1$-receptors observed in the femoral artery observed may reflect a similar adaptation in more distal regions of the muscle vasculature that are in close proximity of the exercising tissue, a concept that is deserving of further study.

The Role of Oxidative Metabolism in Exercise Sympatholysis

The initial observation that $\alpha_1$-adrenergic sensitivity was not different between young and old at the 10-W intensity level presented a need for additional measurements to further examine the putative mechanisms that contribute to functional sympatholysis. Thus the majority of subjects ($n = 10$) returned to the laboratory to repeat the exercise protocol with femoral and arterial catheterization for arteriovenous blood sampling across the exercising leg. This approach allowed PE-induced vasoconstriction to be viewed according to single-leg VO$_2$, which revealed a clear relationship in both young and old (Fig. 4). Although not necessarily reflective of cause and effect, these data suggest that the exercise-intensity-dependent nature of sympatholysis is tightly related to VO$_2$, implying that $\alpha_1$-mediated vasoconstriction during exercise may be due, in part, to the consequences of increasing oxidative metabolism in the exercising leg.

The link between absolute energy demand and sympatholysis is further supported by measurements of leg lactate efflux and venous pH during exercise. Whether viewed in terms of absolute or relative exercise intensity, the exercising leg of older subjects produced more lactate and experienced a lower pH during exercise (Table 3). While the reasons for this elevated lactate in the elderly are not readily apparent, we speculate that this response may be indicative of altered oxidative metabolism in the elderly, such that older subjects relied more heavily on anaerobic metabolism during exercise to achieve the same amount of muscular work. Interestingly, a significant vasoconstriction in response to PE was maintained in the elderly group during exercise, even in the face of this elevated lactate efflux. These findings are in agreement with earlier work in animals, indicating that PE-mediated vasoconstriction is not attenuated by mild acidosis (17) and suggests a minimal contribution of lactate to exercise-induced blunting of $\alpha_1$-adrenergic receptors in the human leg.

Elevations in VO$_2$ as a consequence of increased muscular work may be associated with increased levels of several putative factors previously identified as contributing to functional sympatholysis. Recent studies in hypertensive animals have identified the capacity of reactive oxygen species to attenuate sympathetic vasoconstriction (49), implicating oxidative stress as a potential regulator of sympatholysis. In conjunction with our laboratory’s recent work identifying increased arteriovenous free radical concentration (alkoxyl and alkyl radicals) in the leg during KE exercise (1), it seems reasonable to speculate that oxidative stress may have played a role in the observed loss of $\alpha_1$-adrenergic vasoconstriction during exercise. In addition, although the present data do not include direct measurements of temperature, it has been demonstrated that both tissue and blood temperature rise significantly during KE exercise (10) and correlate with the rise in leg VO$_2$. With the known ability of high temperatures to blunt PE-induced vasoconstriction (16), we speculate that the decline in $\alpha_1$-adrenergic sensitivity in the present study may also be related to exercise-induced thermal effects. Finally, recent studies administering exogenous ATP (12, 33, 34) and other purine nucleotides (34) have collectively identified ATP as a capable of attenuating vasoconstriction to a host of sympathomimetic drugs, leading to the conclusion that ATP may act as a sympatholytic agent during exercise. While data from the present study do not address this mechanism, it is possible that the observed differences in PE-mediated vasoconstriction between young and older groups may be partially attributed to age-related differences in intramuscular and/or intravascular ATP concentration. Certainly, additional study is warranted to further examine the emerging role of this mechanism in the autonomic regulation of blood flow during exercise with advancing age.

Conclusions

The present study has confirmed an age-related decline in $\alpha_1$-adrenergic receptor sensitivity to an exogenous $\alpha_1$-agonist (PE) at rest. Exercise blunted PE-induced vasoconstriction in both young and older subjects, the degree of which was heavily dependent on whether responses are viewed in terms of absolute or relative exercise intensity. These findings question the current concept of reduced functional sympatholysis during exercise with advancing age.

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