α-Adrenergic Vasoconstriction Contributes to the Age-Related Increase in Conduit Artery Retrograde and Oscillatory Shear

Darren P. Casey, Jaume Padilla, Michael J. Joyner

Abstract—Aging is associated with increased retrograde and oscillatory shear in peripheral conduit arteries of humans. Although the mechanisms responsible for these age-related changes are not completely understood, augmented downstream α-adrenergic tone likely plays a significant role in this phenomenon. Therefore, in protocol 1, brachial artery diameter and blood velocity were measured via Doppler ultrasound during (1) rest (control), (2) endogenous norepinephrine release via intra-arterial infusions of tyramine, and (3) α-adrenergic blockade via infusions of phentolamine in young healthy humans (n=12). Tyramine increased brachial artery retrograde (−4.0±1.4 to −9.5±1.4 s⁻¹) and oscillatory shear (0.05±0.02 to 0.18±0.05 arbitrary units), whereas phentolamine abolished retrograde and oscillatory shear (P<0.05). Additionally, in protocol 2, we examined brachial artery shear patterns in young (n=12; 29±2 years) and older (n=13; 69±2 years) healthy adults during (1) rest (control), (2) sympathetic activation via lower body negative pressure, and (3) infusion of phentolamine. At rest, older adults exhibited greater brachial artery retrograde and oscillatory shear (−9.9±2.7 s⁻¹ and 0.11±0.03 arbitrary units, respectively) compared with younger adults (−3.1±1.0 s⁻¹ and 0.05±0.02 arbitrary units, respectively; P<0.05 for both). Lower body negative pressure increased retrograde and oscillatory shear in young (P<0.05), but not older adults (P=0.85–0.97), such that differences between young and older were eliminated (P>0.05). During infusion of phentolamine, retrograde and oscillatory shear were abolished in young adults (P<0.05) and markedly reduced, yet still persistent, in older adults (P<0.01). Our data indicate that α-adrenergic vasoconstriction is a major contributor to age-related discrepancies in conduit artery shear-rate patterns at rest. (Hypertension. 2012;60:1016-1022.)

Key Words: α-adrenergic receptors ■ aging ■ shear rate ■ sympathetic activation

Blood flow patterns within large peripheral conduit arteries (ie, brachial and femoral) commonly present with a triphasic appearance that is characterized by an initial large antegrade flow pattern during systole, followed by a brief episode of retrograde flow early in diastole and subsequent antegrade flow in mid- to late diastole.¹² The pattern of blood flow and the resulting oscillatory (bidirectional blood flow) shear patterns in conduit vessels are thought to influence endothelial cell function. Indeed, in vitro studies using endothelial cell culture and isolated perfused arteries indicate that increased retrograde and oscillatory shear can induce profound proatherogenic effects on endothelial cells, including increased production of nicotinamide adenine dinucleotide phosphate-oxidase- and mitochondria-derived reactive oxygen species, augmented production of endothelin-1, and enhanced expression of adhesion molecules.⁵–¹² Moreover, although limited, there are also data available in humans suggesting that brachial artery endothelium-dependent dilation is impaired after an acute bout of increased retrograde and oscillatory shear.¹³ Evidence in humans suggests that aging is associated with greater retrograde and oscillatory shear in peripheral conduit arteries.¹⁴–¹⁶ Although the mechanisms responsible for these age-related changes are not completely understood, alterations in downstream vascular resistance likely play a significant role in the increase in retrograde and oscillatory shear in conduit arteries of older adults. Indeed, brachial artery retrograde flow is reduced as a result of experimentally induced decreases in downstream resistance in young adults,¹⁷,¹⁸ whereas, conditions that elevate vascular resistance provoke an increase in retrograde flow.¹³,¹⁷,¹⁹,²⁰ Of particular interest to the current study, acute elevations in muscle sympathetic nerve activity (MSNA) are associated with an increase in conduit artery retrograde and oscillatory shear in young males.²⁰ Because MSNA increases with aging,²¹,²² it is possible that an increased α-adrenergic vasoconstriction in resistance vessels contributes to the age-related differences in resting shear-rate patterns in the upstream conduit arteries. Therefore, the aim of the current study was to examine the contribution of α-adrenergic vasoconstriction in resistance
vessels on shear-rate profiles in upstream conduit arteries of young and older adults. We hypothesized that postjunctional α-adrenergic vasoconstriction in young adults and local α-adrenergic blockade in older adults would eliminate age-related differences in resting conduit artery retrograde and oscillatory shear.

Methods

Study Design

Two separate protocols were performed in which brachial artery blood velocity and diameter were measured in order to calculate blood flow and shear rate. In protocol 1, we examined the influence of α-adrenergic vasoconstriction on conduit artery shear-rate patterns in young healthy adults. In protocol 2, we investigated whether α-adrenergic vasoconstriction in resistance vessels contributes to age-related discrepancies in conduit artery shear-rate patterns at rest. All study protocols were approved by the Mayo Clinic Institutional Review Board and performed according to the Declaration of Helsinki. Each subject gave written informed consent before participation.

Subjects

A total of 37 subjects volunteered to participate in 1 of 2 protocols. Studies were performed between 7:00 and 11:00 after an overnight fast and refraining from exercise and caffeine for at least 24 hours. All studies were performed while the subjects rested in the supine position. Protocol 1 included 12 young healthy men (24–40 years). Protocol 2 included a separate group of 12 young (6 men and 6 women; 19–37 years) and 13 older (7 men and 6 women; 61–81 years) healthy subjects. Subjects from both protocols underwent a standard screening and were healthy, nonobese (body mass index≤30 kg m⁻²), nonsmokers, not taking any vasoactive medications, and were sedentary to moderately active. In protocol 2, 4 older subjects were taking Omeprazole (proton pump inhibitor) to treat gastroesophageal reflux (withheld for a minimum of 3 days before study), 1 older subject was taking aspirin (withheld for 1 week before study), and 2 older subjects were taking Synthroid to treat hypothyroidism (withheld 3 days before study). Five older subjects reported taking a daily vitamin. Young women subjects were studied during the early follicular phase of the menstrual cycle or 2 weeks before study, and 2 older subjects were taking Synthroid to treat hypothyroidism (withheld 3 days before study). Five older subjects reported taking a daily vitamin. Young women subjects were postmenopausal and were not taking any form of hormone replacement therapy.

Arterial Catheterization

A 20 gauge, 5 cm (Model RA-04020, Arrow International, Reading, PA) catheter was placed in the brachial artery of the experimental arm under aseptic conditions after local anesthetics (2% lidocaine) for administration of study drugs. The catheter was connected to a 3-port connector in series, as previously described in detail. One port was linked to a pressure transducer positioned at heart level (Model PX600F, Edwards Lifescience, Irvine, CA) to allow measurement of arterial pressure and was continuously flushed (3 mL h⁻¹) with saline with a stop-cock system to enable arterial blood sampling. The remaining 2 ports allowed arterial drug administration.

Heart Rate and Systemic Blood Pressure

Heart rate was recorded via continuous 3 lead ECG. A pressure transducer connected to the arterial catheter measured beat-to-beat blood pressure (Cardiocap/5, DateX-Ohmeda, Louisville, CO)

Forearm Blood Flow

Brachial artery mean blood velocity and brachial artery diameter were determined with a 12 MHz linear-array Doppler probe (Model M12L, Vivid 7, General Electric, Milwaukee, WI). Brachial artery blood velocity was measured throughout each condition with a probe insonation angle previously calibrated to 60°. Brachial artery diameter measurements were obtained at end diastole. Forearm blood flow was calculated as the product of mean blood velocity (cm s⁻¹) and brachial artery cross-sectional area (cm²) and expressed as milliliters per minute (mL min⁻¹).

Pharmacological Infusions

In protocol 1, tyramine (Sigma-Aldrich, St Louis, MO) was administered intraarterially (12 μg (dL forearm volume)⁻¹ min⁻¹ for 3 minutes) to evoke endogenous norepinephrine release and stimulate both α₁ and α₂-adrenoceptors. In protocols 1 and 2, phentolamine mesylate (Bedford Laboratories, Bedford, OH), a nonselective α-adrenoceptor receptor antagonist, was administered to the experimental forearm via brachial artery catheter as a loading dose (10 μg (dL forearm volume)⁻¹ min⁻¹ for 5 minutes) followed by a continuous maintenance dose (25–50 μg min⁻¹). This dose of phentolamine has been shown to effectively inhibit α-adrenergic receptor vasoconstriction. In protocol 1, tyramine (Sigma-Aldrich, St Louis, MO) was administered intraarterially (12 μg (dL forearm volume)⁻¹ min⁻¹ for 3 minutes) to evoke endogenous norepinephrine release and stimulate both α₁ and α₂-adrenoceptors. In protocols 1 and 2, phentolamine mesylate (Bedford Laboratories, Bedford, OH), a nonselective α-adrenoceptor receptor antagonist, was administered to the experimental forearm via brachial artery catheter as a loading dose (10 μg (dL forearm volume)⁻¹ min⁻¹ for 5 minutes) followed by a continuous maintenance dose (25–50 μg min⁻¹). This dose of phentolamine has been shown to effectively inhibit α-adrenergic receptor vasoconstriction.20

Lower Body Negative Pressure

Lower body negative pressure (LBNP) was used to examine the influence of increased sympathetic outflow on conduit artery shear patterns. While supine the lower body of each subject was sealed in an airtight box above the level of the iliac crest. The box was attached to a vacuum source, which allowed for rapid reductions in pressure. During the LBNP trials the pressure was reduced to −20 mm Hg. Hemodynamic variables were continuously recorded for 3 minutes while at the target LBNP pressure (−20 mm Hg). Application of low levels of LBNP (−20 mm Hg) increases MSNA without concurrent changes in heart rate and arterial pressure. Moreover, this level of LBNP increases MSNA in young adults to similar levels observed in older adults at rest (ie, without LBNP).21

Experimental Protocol

Protocol 1

Measurements were collected at rest during control (no drug), α-adrenergic receptor vasoconstriction (via intraarterial infusion of tyramine), and local α-adrenergic blockade (via intraarterial infusion of phentolamine) conditions.

Protocol 2

Measurements were collected at rest during control (no drug), sympathetic stimulation (via LBNP), and local α-adrenergic blockade (via intraarterial infusion of phentolamine) conditions. Due to the long half-life of phentolamine, α-adrenergic blockade trials were always performed last in both protocols. A rest period of 15 minutes was allowed between conditions to ensure reestablishment of baseline hemodynamic variables.

Data Analysis and Statistics

Data were collected at 250 Hz, stored on a computer and analyzed offline with signal processing software (WinDaq, DATAQ Instruments, Akron, OH). Mean arterial pressure was determined from the brachial artery pressure waveform and heart rate was determined from the ECG. Time average mean blood velocity, antegrade mean velocity, and retrograde mean velocity were calculated. Diameter and velocity measures were used to estimate brachial artery shear rates. Mean shear rate (s⁻¹) was defined as 4 · Vm/D, where Vm is mean blood velocity (cm s⁻¹) and D is arterial diameter (cm). For calculations of antegrade and retrograde shear rate, antegrade and retrograde mean blood velocities were used, respectively. Oscillatory shear index is a dimensionless parameter that can be used as an indicator of the magnitude of oscillation and can be defined as follows: Retrograde shear/(Antegrade shear+Retrograde shear). Note that the values for oscillatory shear range from 0 to 0.5, where a value of 0 corresponds to a unidirectional shear rate throughout the cardiac cycle, and a value of 0.5 represents pure oscillation with a time-average shear equal to 0. Forearm vascular conductance was calculated as the ratio between forearm blood flow...
Sympathetic Influence and the Age-Related Discrepancies in Shear Patterns

Under control conditions, older adults demonstrated greater retrograde and oscillatory shear (−9.0±2.4 s\(^{-1}\) and 0.10±0.03 arbitrary units, respectively) compared with younger adults (−2.9±0.6 s\(^{-1}\) and 0.05±0.01 arbitrary units, respectively; \(P<0.05\) for both; Figure 2). Sympathetic activation via LBNP in young, but not older, adults increased retrograde (−2.9±0.6 to −5.9±1.3 s\(^{-1}\); \(P<0.05\)) and oscillatory (0.05±0.01 to 0.09±0.02 arbitrary units, \(P<0.05\)) shear, such that differences between young and older were eliminated (\(P=0.24\) for retrograde and 0.42 for oscillatory shear).

\(\alpha\)-adrenergic blockade via phentolamine resulted in a substantial increase in forearm blood flow and conductance in young and older adults (Table 3). In turn, mean and antegrade shear were greater in young and older adults during phentolamine infusion compared with control conditions (\(P<0.01\), Table 3). As depicted in Figure 2, during \(\alpha\)-adrenergic blockade, retrograde and oscillatory shear were abolished in young adults (\(P<0.05\)) and markedly reduced, yet still persistent, in older adults (\(P<0.01\)). Indeed, retrograde shear was greater in older compared with young adults during infusion of phentolamine (\(P<0.05\), Figure 2).

Discussion

The primary novel findings of the present study are as follows: (1) endogenous norepinephrine release in the forearm of young men increased upstream conduit artery retrograde and oscillatory shear, (2) sympathetic activation increased retrograde and oscillatory shear in the brachial artery of young, but not older, adults, such that age-related differences were no longer apparent, (3) brachial artery retrograde and oscillatory shear were abolished in younger adults and reduced in older adults during \(\alpha\)-adrenergic blockade, and (4) despite drastic changes in brachial artery blood flow and shear-rate patterns (increased antegrade and decreased retrograde shear) during \(\alpha\)-adrenergic blockade, retrograde shear remained significantly higher in older versus younger adults. Taken together our data indicate that \(\alpha\)-adrenergic vasoconstriction contributes, in part to age-related increases in conduit artery retrograde and oscillatory shear at rest.

The finding that low levels of LBNP (−20 mm Hg) can increase retrograde and oscillatory shear in young adults is in agreement with previous data.\(^{20}\) Padilla and colleagues\(^{20}\) demonstrated that progressive increases in MSNA associated with graded LBNP (−10 to −40 mm Hg) elicit commensurate increases in retrograde and oscillatory shear in young men. Herein, taking a pharmacological approach, our data further support the role of the sympathetic nervous system in dictating conduit artery blood flow profiles. We demonstrated in young men that increased forearm resistance (via endogenous norepinephrine release) promotes enhanced retrograde and oscillatory shear at the brachial artery; whereas, reciprocally, decreased resistance (via \(\alpha\)-adrenergic blockade) completely abolishes retrograde and oscillatory shear (Figure 1).

Importantly, our current results suggest that sympathetic activation increases retrograde and oscillatory shear in young

### Table 1. Forearm Hemodynamics and Shear-Rate Patterns at Rest During Control, Tyramine, Phentolamine in Young Men (n=12)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Tyramine</th>
<th>Phentolamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>90±1</td>
<td>91±2</td>
<td>87±2*</td>
</tr>
<tr>
<td>Forearm vascular conductance, mL \cdot min(^{-1}) \cdot 100 mm Hg(^{-1})</td>
<td>136±31</td>
<td>90±20*</td>
<td>369±48*</td>
</tr>
<tr>
<td>Brachial artery diameter, cm</td>
<td>0.46±0.01</td>
<td>0.46±0.01</td>
<td>0.47±0.01*</td>
</tr>
<tr>
<td>Mean velocity, cm \cdot s(^{-1})</td>
<td>11.8±2.4</td>
<td>8.1±1.7*</td>
<td>29.8±3.1*</td>
</tr>
<tr>
<td>Mean shear rate, s(^{-1})</td>
<td>101±20.1</td>
<td>70.3±13.9*</td>
<td>254.2±25.7*</td>
</tr>
<tr>
<td>Antegrade shear velocity, cm \cdot s(^{-1})</td>
<td>12.2±2.4</td>
<td>9.1±1.6*</td>
<td>29.8±3.1*</td>
</tr>
<tr>
<td>Retrograde shear velocity, cm \cdot s(^{-1})</td>
<td>−0.4±0.1</td>
<td>−1.0±0.3*</td>
<td>0.0±0.0*</td>
</tr>
</tbody>
</table>

\(^{*}P<0.01\) vs Control.

\(^{1}P<0.05\) vs Control.
men, to the extent that age-related discrepancies were abolished by tyramine. Of interest, in the present study retrograde and oscillatory shear were unaltered during LBNP in older adults. The lack of change in the conduit artery shear-rate patterns in older adults with LBNP might be related to an already elevated retrograde and oscillatory blood flow present at rest before sympathetic activation. That is, it is possible that with aging the influence of sympathetic nerve activity on conduit artery retrograde and oscillatory flow has reached a ceiling effect such that further sympa-ho-excitation does not produce additional changes in flow profiles. Alternatively, it is also plausible that $\alpha$-adrenergic responsiveness is diminished in the resistance vasculature of older adults. Indeed, it has been well characterized that aging is associated with a reduction in forearm and leg postjunctional $\alpha$-adrenergic responsiveness to endogenous norepinephrine release.\(^{30,31}\)

**Table 2. Subject Characteristics for Protocol 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young (n=12)</th>
<th>Older (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27±2</td>
<td>69±2*</td>
</tr>
<tr>
<td>Male/Female</td>
<td>6/6</td>
<td>7/6</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174±2</td>
<td>170±3</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75±3</td>
<td>76±4</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>24.7±0.9</td>
<td>26.1±0.9</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>129±3</td>
<td>142±3*</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79±2</td>
<td>84±2</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>96±2</td>
<td>103±2*</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>143±5</td>
<td>186±6*</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>71±3</td>
<td>110±6*</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>53±4</td>
<td>53±6</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>89±8</td>
<td>90±6</td>
</tr>
</tbody>
</table>

Values are means±SE. BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; LDL, low density lipoprotein, and HDL, high density lipoprotein.  

*P<0.05 vs young.

**Figure 2.** Brachial artery retrograde shear rate and oscillatory shear index at rest during control, sympathetic activation via lower body negative pressure (LBNP), and intraarterial administration of phentolamine (nonspecific $\alpha$-adrenergic antagonist) in young and older subjects (Protocol 2). Values are means±SE. *P<0.05 versus young; †P<0.01 versus control.
Our initial hypothesis was that α-adrenergic blockade with phentolamine would reduce retrograde and oscillatory shear in young and older adults and thus eliminate any age-related differences. The current findings demonstrate that retrograde and oscillatory shear are abolished in young adults and substantially reduced in older adults during α-adrenergic blockade (Figure 2). However, the age-related difference in retrograde shear persisted despite the removal of α-adrenergic vasoconstrictor tone. This is an important observation as it suggests that other factors, independent of α-adrenergic vasoconstrictor tone, likely contribute to the age-related increases in conduit artery retrograde shear. Along these lines, we recently found that nitric oxide synthase inhibition in the forearm circulation of young, but not older, subjects increased retrograde and oscillatory shear, thus suggesting that reduced nitric oxide bioavailability in the resistance vessels contributes, in part, to age-related discrepancies in resting shear patterns.15 Taken together, we propose that with aging increased retrograde shear in conduit arteries during rest is due to combined increased α-adrenergic vasoconstriction and reduced nitric oxide bioavailability in the downstream resistance vasculature. However, it is possible that alterations in β-adrenergic–mediated vasodilation might also play a role in the age-related differences in retrograde shear during the phentolamine trials. In this context, age-associated reductions in β-adrenergic vasodilation have been observed in rat skeletal muscle arterioles33 and human limbs.34 An attenuated β-adrenergic vasodilation may serve to increase downstream resistance and partially explain the retrograde shear that persists in older adults during α-adrenergic blockade. Further research needs to examine the contribution of the β-adrenergic receptors as well as other vasoactive factors that are influenced by aging (eg, endothelin-1, angiotensin II).

Experimental Considerations

In the present study we did not directly assess MSNA under control or LBNP conditions. Therefore, we were not able to quantify the magnitude of sympathetic activation in the young and older adults during LBNP. However, low levels of LBNP (−20 mm Hg) have consistently been shown to be effective in increasing MNSA in men and women.20,21,26,35 Of particular interest to the current study, LBNP applied at −20 mm Hg increases MSNA in young adults to similar levels observed in older adults at rest.21 Moreover, the change in MSNA in response to LBNP is not different in young and older adults.31 The use of a nonspecific α-adrenergic antagonist (phentolamine) in the current study did not allow us to discern the relative roles of α1- and α2-adrenergic receptors in the age-related differences in resting shear patterns. In this regard, it has been reported in young healthy men that α1-adrenergic receptors have a greater contribution to basal forearm vascular tone compared with α2-adrenergic receptors.36 Further research needs to establish the relative contribution of α1- and α2-adrenergic receptors in controlling shear-rate patterns with aging.

Lastly, previous data from our laboratory37 and others38 demonstrate that, in young women, high MSNA and exogenous infusion of norepinephrine does not necessarily translate into elevated peripheral vascular resistance as it does in men. Therefore, it is plausible that sex-specific differences exist in conduit artery shear patterns of young men and women. Along these lines, there was a trend for a lower oscillatory shear in the young women (n=6) compared with the young men (n=6) under control conditions in protocol 2 (0.03±0.01 versus 0.06±0.02 arbitrary units, P=0.09). To this point, future studies should address the interactions between sex, vascular resistance, and conduit shear-rate patterns in humans.

Perspectives

Aging in healthy humans is characterized by a progressive activation of the sympathetic nervous system. In turn, chronically elevated sympathetic nerve activity is associated with several cardiovascular diseases.39 Our findings highlight the influence that sympathetic activation and α-adrenergic vasoconstriction have on conduit artery hemodynamics and shear...
patterns. Importantly, our data suggest that α-adrenergic vasoconstriction substantially contributes to the increased magnitude of retrograde and oscillatory shear present in peripheral conduit arteries of older adults, which in turn may contribute to the deleterious alterations in endothelial function commonly observed in this population.40,41 Further research needs to evaluate whether increased cardiac sympathetic activity with aging leads to alterations in blood flow profiles in the coronary arteries where the clinically significant lesions are most likely to occur.

Conclusions
In young adults, acute sympathetic stimulation via LBNP and norepinephrine release via tyramine administration increased conduit artery retrograde and oscillatory shear to similar levels observed in older adults. During α-adrenergic blockade, retrograde and oscillatory were abolished in young adults and markedly reduced, however, still persistent in older adults. Collectively, the present investigation provides the first evidence that α-adrenergic vasoconstriction contributes, in part, to age-related increases in conduit artery retrograde and oscillatory shear at rest.

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Disclosures
None.

References

### What Is New?
- Pharmacological stimulation of α-adrenergic receptors in the forearm of young men increased upstream conduit artery retrograde and oscillatory shear.
- Sympathetic activation increased retrograde and oscillatory shear in the brachial artery of young, but not older, adults, such that age-related differences were no longer apparent.
- Brachial artery retrograde and oscillatory shear were abolished in younger adults and reduced in older adults during α-adrenergic blockade.
- Despite drastic changes in brachial artery blood flow and shear-rate patterns (increased antegrade and decreased retrograde shear) during α-adrenergic blockade, retrograde shear remained significantly higher in older versus younger adults.

### What Is Relevant?
- Increased α-adrenergic vasoconstriction in the resistance vessels contributes, in part, to age-related discrepancies in resting shear patterns, thus identifying a potential mechanism for increased risk of atherosclerotic disease in conduit arteries.

### Summary
α-adrenergic vasoconstriction contributes, in part, to age-related discrepancies in conduit artery shear-rate patterns at rest.
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