Effect of SR Manipulation on Conduit Artery Dilation in Humans


Abstract—The impact of manipulating shear stress on conduit artery vasodilation has not been comprehensively described in vivo. We hypothesized that manipulation of SR through the brachial and radial arteries would be associated with corresponding changes in diameter. We performed a series of studies involving the following: (1) leg cycle exercise at increasing intensities (≈70 and 85% maximum heart rate [HRmax]) with simultaneous bilateral measurement of SR in the radial arteries; (2) leg cycle exercise for 30 minutes at 80% HRmax with simultaneous bilateral measurement of velocity and diameter in the brachial arteries; and (3) bilateral forearm heating for 30 minutes with simultaneous bilateral measurement of brachial artery diameter and blood velocity. Cycling and forearm heating interventions were performed in the presence of unilateral cuff inflation throughout the experiment, or starting during the intervention (15 minutes), to manipulate SR responses. Cuff placement was associated with lower radial artery SR responses (cuffed versus uncuffed, 248±49 versus 349±105 L/s 85% HRmax; P<0.01), and diameter responses were similarly attenuated (2.45±0.30 versus 2.78±0.20 mm 85% HRmax; P<0.05). Exercise performed at 80% HRmax in the presence of unilateral cuff inflation also reduced brachial artery SR (cuffed versus uncuffed; 258±107 versus 454±157 L/s; P<0.01) and diameter (4.35±0.39 versus 4.20±0.45 mm). Finally, cuff inflation decreased the impact of forearm heating on brachial SR (cuffed versus uncuffed; 262±97 versus 440±106 L/s; P<0.01) and diameter (4.35±0.54 versus 4.87±0.47 mm; P<0.05). Similar significant differences between the cuffed and uncuffed limbs in SR and diameter were observed when cuff inflation occurred during exercise or heating. Our findings strongly implicate SR as an important stimulus to increase conduit artery diameter in humans. (Hypertension. 2013;61:143-150.)

Key Words: SR ■ high-resolution ultrasound ■ cardiovascular ■ exercise intensity ■ exercise training ■ cardiovascular disease

Exercise decreases primary and secondary cardiovascular events,1,2 effects that cannot be entirely accounted for by modification of traditional risk factors.3,4 Animal studies implicate shear stress as a key stimulus to the release of paracrine hormones, including NO, from the endothelium during exercise bouts.5-7 Episodic exposure to elevations in shear stress may explain the cardioprotective effects of exercise training through direct effect on the vascular wall.8,9

Previous studies in humans have assessed the relationship between shear rate (SR) and conduit artery diameter by increasing SR using heating10 or exercise10,11 or responses to different periods of arterial occlusion.12,13 These studies are complimented by recent data from Padilla et al,10 who demonstrated that matched SR changes associated with leg exercise and forearm heating increase brachial artery dilation to a similar extent. Although this evidence suggests that shear stress may play a role in conduit artery dilation in humans, an approach that attenuates shear as a stimulus, without affecting other potential vasodilator stimuli, is necessary to establish that SR is a key stimulus that induces conduit artery diameter change in humans.

In the present study we adopted 3 general strategies to comprehensively examine the hypothesis that shear stress manipulation would alter conduit artery dilation. Leg exercise was performed at distinct intensities in the same subjects to assess dose–response relationships, with shear and diameter measured during the exercise bouts (study 1). We assessed the impact of increased shear and shear attenuation by using partial cuff inflation on 1 forearm during simultaneous bilateral measures in the radial arteries. In a second study, we assessed the impact of cycle ergometer exercise (at 80% maximum heart rate [HRmax]) on brachial artery shear and dilation using similar techniques (study 2). Finally, to address the impact of shear manipulation in the absence of exercise, we heated both forearms simultaneously by placement in water baths (42°C) and measured consequent changes in brachial shear and diameter, with a cuff inflated to manipulate shear through 1 arm (study 3). We also repeated the latter studies...
using cuff inflation during, instead of throughout, the cycle and heating interventions. In all of the experiments, we used within-subjects simultaneous measures to dissect the effects of SR manipulation on conduit artery diameter in the absence of central or reflex hemodynamic effects.

Methods

Ethical Approval
All of the study procedures were approved by the human research ethics committees at the University of Western Australia or Liverpool John Moores University. Written, informed consent was obtained from all of the subjects, and studies conformed to the Declaration of Helsinki.

Subject Characteristics
Forty-four young healthy male subjects (25±3 years) were recruited to participate in 1 of 5 experiments. Subjects were recreationally active (≤2 hours of physical activity per week), and all were free from cardiovascular disease, diabetes mellitus, insulin resistance, and cardiovascular risk factors. Subjects who smoked or were on medication of any type were excluded.

Study Designs

Cycle Exercise and Cuffed and Uncuffed Forearms: Dose Response and Role of SR in Radial Artery Dilation
Eight subjects performed 2 separate bouts of exercise on a cycle ergometer (Monark 874E) at 70% and 85% HRmax. Attendances were separated by >48 hours, with all of the bouts completed within 14 days of the initial test and each session performed at the same time of day. The order of tests (70% and 85%) was randomized among subjects. Radial artery diameter and velocity were collected simultaneously in both forearms at rest and between 10 and 15 minutes during exercise. Immediately before exercise a pneumatic cuff was placed around 1 forearm, distal to the probe location, and inflated to 60 mm Hg, whereas the contralateral arm remained uncuffed during cycle exercise.

Cycle Exercise and Forearm Cuff Inflation Throughout Exercise: Role of SR in the Brachial Artery
Ten subjects, distinct from those studied above, were recruited to undertake 30 minutes of cycle exercise (Monark 874E) at 80% HRmax. Throughout the exercise bout a pneumatic cuff was placed around 1 forearm immediately below the cubital crease and inflated to 60 mm Hg. The contralateral arm remained uncuffed during cycle exercise. Simultaneous brachial artery diameter and velocity values were collected immediately before exercise and before cuff inflation, and at the 15- and 25-minute marks during exercise. Previous studies have demonstrated that placement and inflation of a forearm cuff attenuates upstream brachial arterial SR.14-16

Cycle Exercise and Cuff Inflation Midexercise: Role of SR in the Brachial Artery
Nine subjects (distinct from those studied above) undertook 30 minutes of cycle exercise (Monark 874E) at 80% HRmax. A pneumatic cuff was placed around 1 forearm and inflated to 60 mm Hg, 15 minutes after the onset of cycle exercise. Simultaneous bilateral brachial artery diameter and velocity values were collected immediately before the onset of exercise and during exercise, at 10 minutes (and before cuff inflation), and after cuff inflation (ie, between 20 and 25 minutes). This study was performed to examine whether brachial artery dilation could be reversed by locally changing SR levels during exercise.

Bilateral Forearm Heating and Forearm Cuff Inflation Throughout: Role of (Nonexercise) SR
An additional 8 subjects underwent 30 minutes of bilateral forearm warm water immersion (42°C). A pneumatic cuff was again positioned and inflated around 1 forearm while the contralateral arm remained uncuffed. The pneumatic cuff was inflated to 100 mm Hg based on pilot studies and our previous published data indicating that this level of inflation affects mean SR during heating.17 Simultaneous bilateral recordings of brachial artery diameter and velocity were again collected immediately before heat application, and at the 15- and 25-minute marks during the intervention.

Bilateral Forearm Heating and Forearm Cuff Inflation Midheating: Role of (Nonexercise) SR
An additional 9 subjects undertook a similar protocol to that described above, involving 30 minutes of bilateral forearm heating. A pneumatic cuff was placed around 1 forearm and inflated to 100 mm Hg after 15 minutes of forearm immersion (42°C). Simultaneous bilateral brachial artery diameter and velocity values were collected before the onset of heating and during heating, at 10 minutes (and before cuff inflation), and after cuff inflation (ie, between 20 and 25 minutes). This study was performed to examine whether brachial artery dilation could be reversed by locally changing SR levels during forearm heating.

Experimental Procedures
All of the experiments were performed in a quiet, temperature-controlled laboratory. Subjects were fasted for a period of 6 hours and abstained from alcohol consumption and exercise for a minimum 18 hours before the commencement of each intervention.

Assessment of Radial and Brachial Artery Diameter and Velocity
After 20 minutes of rest, radial or brachial artery diameter and velocity were simultaneously assessed using a 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (T3000; Terson, Burlington, MA). Recordings commenced after optimization of the longitudinal B-mode image of the lumen-arterial walls. Concurrently, Doppler velocity assessments were collected using the lowest possible insonation angle (always <60°). The arms were positioned at heart level, and this position of the arms was identical bilaterally and not different across the various tests. Also, the same posture was used to assess diameters before and during exercise and heating.

Diameter and SR Analysis
Analysis of artery diameter was performed using custom-designed edge detection and wall-tracking software, which is independent of investigator bias and has previously been comprehensively described.18,19 From synchronized diameter and velocity data, blood flow (the product of lumen cross-sectional area and Doppler velocity) was calculated at 30 Hz. SR (an estimate of shear stress without viscosity)13,20 was calculated as 4 times mean blood velocity/vesSEL diameter. Reproducibility of diameter measurements using this semiautomated software is significantly better than manual methods, reduces observer error and bias significantly, and possesses an intraobserver coefficient of variation of 6.7%.18

Statistics
Statistical analysis was performed using SPSS 18.0 (SPSS, Chicago, IL) software. All of the data are reported as mean±SD unless stated otherwise, and statistical significance was assumed at P<0.05. Two-factor ANOVAs with repeated measures (with time and intensity or cuff placement as the independent factors) were performed. Post hoc analysis t tests were used where significant values were found.

Results
Subjects recruited to each of the experimental protocols were similar in terms of age and hemodynamics (Table 1).

Cycle Exercise and Cuffed and Uncuffed Forearms: Dose Response and Role of SR in Radial Artery Dilation

SR Responses
Cycle exercise significantly increased mean radial artery SR in both arms (2-way ANOVA main effect time P<0.01), although
the increase in shear was significantly attenuated in the cuffed arm (Figure 1A; 2-way ANOVA time*cuff interaction, \( P<0.005 \)). Retrograde SR increased significantly from baseline to cycling exercise; post hoc analysis revealed that exercise increased retrograde SR in the cuffed arm, whereas no changes were observed in the uncuffed arm (Table 2).

**Radial Artery Diameter Responses**

A significant interaction effect revealed the presence of a different time-dependent response between the limbs \((P<0.01\); Figure 1B). Whereas significant increases in radial artery diameter were observed in the uncuffed arm during exercise, changes in radial artery diameter in the cuffed arm did not reach statistical significance (Figure 1B).

### Table 1. Subject Characteristics for the 5 Experimental Protocols

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cycle±Cuff (n=8)</th>
<th>Cycle±Cuff (n=10)</th>
<th>Cycle±Cuff (Midpoint; n=9)</th>
<th>Forearm Heating±Cuff (n=8)</th>
<th>Forearm Heating±Cuff (Midpoint; n=9)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>22±1</td>
<td>24±2</td>
<td>28±4</td>
<td>23±3</td>
<td>24±2</td>
<td>NS</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>134±17*</td>
<td>115±27</td>
<td>106±28</td>
<td>119±7</td>
<td>125±8</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>64±6</td>
<td>71±11</td>
<td>66±12</td>
<td>65±8</td>
<td>62±11</td>
<td>NS</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>74±7</td>
<td>85±24</td>
<td>94±26</td>
<td>61±6</td>
<td>61±5</td>
<td>NS</td>
</tr>
</tbody>
</table>

SBP indicates systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; NS, not significant. Values are mean±SD.

*SBP under this condition was recorded at the ankle.

### Cycle Exercise and Forearm Cuff Inflation Throughout Exercise: Role of SR in the Brachial Artery

**SR Responses**

SR data for 1 subject were removed from the analysis because of inadequate edge detection of the velocity envelope. A 2-way ANOVA revealed a significant impact of cuff placement on mean SR responses across time \((P<0.01)\), and \( t \) tests revealed significant differences between the cuffed and uncuffed arms at 15 \((P<0.05)\) and 25 minutes \((P<0.01\); Figure 2A). A repeated-measures ANOVA revealed a significant difference in retrograde SR across the 3 time points in the cuffed arm \((P<0.05)\) with \( t \) tests revealing a significant increase relative to baseline at 15 minutes \((P<0.01)\) and 25 minutes \((P<0.01)\), whereas no change was evident in the uncuffed arm (Tables 3 and 4).

**Brachial Artery Diameter Responses**

A significant interaction effect revealed the presence of a different time-dependent diameter response between the limbs \((P<0.01\); Figure 2B). In the uncuffed arm, diameter increased significantly compared with baseline at 25 minutes \((P<0.01)\), whereas increases in the cuffed arm were not significant at any time point. Direct comparison between the limbs revealed a significant difference between the limbs at 25 minutes \((P<0.05)\).

### Cycle Exercise and Forearm Cuff Inflation Midexercise: Role of SR in the Brachial Artery

**SR Responses**

A 2-way ANOVA revealed a significant impact of cuff placement on mean SR responses across time \((P<0.01)\), and \( t \) tests revealed significant differences between the cuffed and uncuffed arms at 25 minutes \((P<0.05\); Figure 3A). Post hoc \( t \) tests revealed no difference in mean SR between the arms at rest or at 10 minutes, when both arms were uncuffed. However, after cuff inflation, SR in the cuffed arm decreased and was significantly lower compared with the uncuffed arm at 20 to 25 minutes \((P<0.05\); Figure 3A).

**Brachial Artery Diameter Responses**

The changes in mean SR as a result of cuff placement induced significant changes in brachial artery diameter that followed a similar pattern. A 2-way ANOVA demonstrated a significant impact of (midpoint) cuff inflation on the diameter response across time \((P<0.01)\). The changes in diameter were similar between both arms during the first 15 minutes before cuff inflation \((P<0.05)\). However, unilateral cuff inflation resulted...
in a decrease in brachial artery diameter toward resting baseline levels, whereas diameter continued to increase in the uncuffed limb (Figure 3B).

**Bilateral Forearm Heating and Forearm Cuff Inflation Throughout Heating: Role of (Nonexercise) SR**

**SR Responses**
A 2-way ANOVA revealed a significant impact of cuff placement on SR responses across time ($P<0.01$), and $t$ tests revealed differences between the arms at all of the time points (15 minutes, $P<0.01$; 25 minutes, $P<0.01$; Figure 4A). Retrograde SR decreased significantly in the uncuffed arm across the 30 minutes ($P<0.01$); however, there was no change in the cuffed arm (Table 3).

**Brachial Artery Diameter Responses**
The distinct mean SR response as a result of cuff placement induced significant differences in brachial artery diameter between the limbs (2-way ANOVA, $P<0.05$ main effect for cuff placement; Figure 4B). Direct comparison between the limbs revealed differences at 15 ($P<0.05$) and 25 minutes ($P<0.05$), but not at baseline.

**Bilateral Forearm Heating and Forearm Cuff Inflation Midheating: Role of (Nonexercise) SR**

**SR Responses**
A 2-way ANOVA revealed a significant impact of cuff placement on mean SR responses across time ($P<0.01$; Figure 5A). Post hoc $t$ tests revealed no differences in mean SR between the arms at rest or at 10 minutes, that is, when both arms were uncuffed. After cuff inflation, SR in the cuffed arm decreased significantly compared with 10 minutes ($P<0.01$), and there was a significant difference between arms at 20 to 25 minutes ($P<0.01$; Figure 5A).

**Brachial Artery Diameter Responses**
The changes in mean SR as a result of cuff placement were accompanied by significant changes in brachial artery diameter that followed a similar pattern. A 2-way ANOVA demonstrated a significant impact of (midpoint) cuff inflation on the diameter change across time ($P<0.05$). The changes in diameter were similar between both arms during the first 15 minutes, with significant increases in diameter evident in both arms ($P<0.01$). However, unilateral cuff inflation resulted in a decrease in brachial artery diameter compared with 10 minutes ($P<0.05$) in the cuffed arm. A significant difference was therefore evident between the arms at 20 to 25 minutes ($P<0.01$; Figure 5B).

### Table 2. Mean, Anterograde, and Retrograde Shear Rate (1/s) Data During Cycling Exercise at Different Intensities

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Status</th>
<th>Rest</th>
<th>70%</th>
<th>85%</th>
<th>$P$ Value, 1-Way</th>
<th>$P$ Value, 2-Way Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>Cuffed</td>
<td>122±76</td>
<td>209±82</td>
<td>248±49</td>
<td>$&lt;0.01$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Uncuffed</td>
<td>121±66</td>
<td>295±91</td>
<td>349±105</td>
<td>$&lt;0.01$</td>
<td></td>
</tr>
<tr>
<td>Antegrade</td>
<td>Cuffed</td>
<td>130±70</td>
<td>253±62</td>
<td>303±44</td>
<td>$&lt;0.01$</td>
<td>NS ($P=0.06$)</td>
</tr>
<tr>
<td></td>
<td>Uncuffed</td>
<td>130±59</td>
<td>311±79</td>
<td>363±92</td>
<td>$&lt;0.01$</td>
<td></td>
</tr>
<tr>
<td>Retrograde</td>
<td>Cuffed</td>
<td>−8±9</td>
<td>−45±22</td>
<td>−56±26</td>
<td>$&lt;0.01$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td></td>
<td>Uncuffed</td>
<td>−8±9</td>
<td>−16±19</td>
<td>−15±15</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS indicates not significant. Data are mean±SD.

### Discussion
The aim of the present study was to assess the effects of SR manipulation on conduit arterial diameter in vivo. Our experimental approaches involved within-subject experimental
Table 3. Mean, Anterograde, and Retrograde Shear Rate Data (1/s) During the Cycling Exercise and Forearm Heating Protocols

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Cuffed</td>
<td>136±94</td>
<td>254±118</td>
<td>258±107 &lt;0.05</td>
<td>&lt;0.01</td>
<td>149±87</td>
<td>230±90</td>
<td>262±97 &lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Uncuffed</td>
<td>141±50</td>
<td>380±169</td>
<td>454±157 &lt;0.01</td>
<td>&lt;0.01</td>
<td>151±89</td>
<td>392±111</td>
<td>440±106 &lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antegrade</td>
<td>146±87</td>
<td>305±121</td>
<td>304±114 &lt;0.01</td>
<td>&lt;0.01</td>
<td>153±85</td>
<td>231±91</td>
<td>264±96 NS &lt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Uncuffed</td>
<td>153±48</td>
<td>390±163</td>
<td>462±148 &lt;0.01</td>
<td>&lt;0.01</td>
<td>156±86</td>
<td>392±111</td>
<td>440±106 &lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Retrograde</td>
<td>-11±11</td>
<td>-52±35</td>
<td>-46±21 NS &lt;0.01</td>
<td>&lt;0.01</td>
<td>-4±3</td>
<td>-2±3</td>
<td>-2±3 NS &lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Uncuffed</td>
<td>-12±17</td>
<td>-10±13</td>
<td>-8±16 NS</td>
<td></td>
<td>-5±6</td>
<td>0±0</td>
<td>0±0 &lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

NS indicates not significant. Data are mean±SD.
placement. It is possible that brachial artery diameter changes may occur in response to changes in either of these variables.14,16 Our findings indicate that cuff placement had a significant impact on brachial and radial artery retrograde shear during leg exercise but not during forearm heating. Cuff placement affected antegrade shear under all conditions. Because artery diameter was similarly affected in response to these interventions, data might imply that manipulation of antegrade flows is a more important stimulus to brachial diameter dilation than retrograde flows, but further studies that are specifically directed at answering this question will be required.

In the present study, leg exercise induced upper limb conduit artery dilation despite the likelihood of increased activation of the sympathetic nervous system in the inactive upper limbs. Some evidence suggests that increased sympathetic nervous system activity is associated with acute impairment in brachial artery vasodilator function.26–28 However, sympathetic nervous system activity is more effective in controlling resistance vessels than conduit arteries, where it has limited impact on baseline diameter.29 In any case, impacts of changes in the sympathetic nervous system or circulating factors would arguably be similar between the limbs, and our experimental approach involving simultaneous bilateral measurements effectively eliminates such factors.

The clinical relevance of our findings relates to the impact of repeated increases in shear stress on the vasculature. It has been suggested recently that the direct effect of repeated episodic increases in shear stress on the vasculature may contribute to the beneficial effect of exercise training on cardiovascular risk.30 In this context, Tinken et al.14 concluded recently that endothelium-dependent vasodilation is increased in the brachial artery immediately after acute bouts of cycle and handgrip exercise. When increases in shear during exercise were attenuated by unilateral pneumatic cuff inflation, increases in endothelial function were abolished. This study suggests that increases in shear stress during exercise can be associated with enhanced endothelial function, a finding endorsed by pharmacological blockade studies, which indicate that NO-mediated vasodilation occurs in forearm conduit31 and resistance32 arteries in response to increases in shear stress associated with handgrip and cycle exercise. It was also observed recently that increases in shear stress are an obligatory component of training-induced endothelial cell adaptation.15 The findings of the current study indicate that manipulation of shear stress during acute interventions modifies conduit artery dilator responses, which are likely endothelium-dependent.

Although our studies successfully manipulated shear stress and modulated endothelial function, they were performed in young healthy men and we cannot extrapolate our findings to other groups. The impact of shear stress manipulations on conduit diameter responses in subjects with endothelial dysfunction has not, to our knowledge, been investigated previously. Another potential limitation of our study is that we cannot rule
out the potential impact of a veno-arteriolar reflex, the proposal that venous distension elicits a local reflex increase in arterial vasoconstriction. The presence of such a response may have contributed to our findings, although evidence for such a reflex in humans is scant. Another limitation is that we reported SR rather than shear stress. Although changes in viscosity may have occurred between experimental conditions, the results of our studies involved within-subject comparison with simultaneous assessments of the arterial diameter. We contend that these experimental design features have effectively controlled for any possible impact of viscosity in our study. Finally, it would have been ideal if our cuffing interventions had completely abolished increases in shear so that we could identify whether factors other than shear contribute to any residual impacts of our interventions on diameter change. Given that we were unable to achieve such abolition, we cannot definitively exclude factors other than shear stress as contributors to conduit artery dilation in response to heating and cycle exercise. Nonetheless, the consistency of our findings, across 5 distinct experimental manipulations, gives us confidence to conclude that shear is an important in vivo physiological determinant of conduit artery vasodilation in humans.

Perspectives

Our findings strongly implicate shear stress as a key stimulus to increased conduit artery diameter in humans and suggest that exercise training induces vascular adaptation via repeated shear stress effects. The observation that upper limb diameters change during leg exercise adds weight to systemic effects of exercise on the vasculature. The impact of heating on shear and diameter further reinforces the role of shear modulation versus non-shear-mediated impacts of exercise. Our findings may have potential clinical relevance to vascular disease and, specifically, the effects of exercise training on arterial health, function, and adaptation. Future studies should examine the impact of shear stress manipulations in groups with impaired endothelial function, such as cardiovascular disease or risk factors (eg, hypertension).

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Disclosures

None.

References


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