Sympathetic vasomotor control does not explain the change in femoral artery shear rate pattern during arm-crank exercise

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Thijssen DH, Green DJ, Steendijk S, Hopman MT. Sympathetic vasomotor control does not explain the change in femoral artery shear rate pattern during arm-crank exercise. Am J Physiol Heart Circ Physiol 296: H180–H185, 2009. First published November 21, 2008; doi:10.1152/ajpheart.00686.2008.—During lower limb exercise, blood flow through the resting upper limbs exhibits a change characterized by increased anterograde flow during systole, but also large increases in retrograde diastolic flow. One explanation for the retrograde flow is that increased sympathetic nervous system (SNS) tone and concomitant increased peripheral resistance generate a rebound during diastole. To examine whether the SNS contributes to retrograde flow patterns, we measured femoral artery blood flow during arm-crank exercise in 10 healthy men (31 ± 4 yr) and 10 spinal cord-injured (SCI) subjects who lack sympathetic innervation in the legs (33 ± 5 yr). Before, and every 5 min during 25-min arm-crank exercise at 50% maximal capacity, femoral artery blood flow and peak anterograde and retrograde shear rate were assessed using echo Doppler sonography. Femoral artery baseline blood flow was significantly lower in SCI compared with controls. Exercise increased femoral artery blood flow in both groups (ANOVA, P < 0.05), whereas leg vascular conductance did not change during exercise in either group. Mean shear rate was lower in SCI than in controls (P < 0.05). Peak anterograde shear rate was higher in SCI than in controls (P < 0.05), whereas peak retrograde shear rate did not differ between groups. Arm-crank exercise induced an increase in peak anterograde and retrograde shear rate in the femoral artery in controls and SCI subjects (P < 0.05). This suggests that the SNS is not obligatory to change the flow pattern in inactive regions during exercise. Local mechanisms may play a role in the arm-crank exercise-induced changes in flow pattern in the femoral artery.

inactive areas; shear pattern

AT THE ONSET OF EXERCISE, substantial cardiovascular adjustments are necessary to continue exercise for more than a few seconds (6). To optimally meet the increased metabolic demands of the contracting muscles, blood flow to inactive regions is relatively decreased, resulting in a net redistribution of blood toward vascular beds in metabolically active regions (1, 6, 21). Recent studies suggest that changes in the pattern of blood flow in inactive areas during exercise may have important effects on exercise training-mediated improvements in vascular function in these nonactive regions (11, 12). Green et al. (11) recently observed that, during lower limb cycle exercise, brachial artery blood flow in the resting upper limbs exhibits an oscillatory pattern of anterograde flow during systole, followed by substantial retrograde diastolic flow. This reproducible change in blood flow pattern during cycling exercise results in a shear rate-mediated release of endothelium-derived nitric oxide (NO) (10, 11). The synthesis of NO is of special interest, given the anti-atherogenic properties of this molecule and its proposed link with vascular health. Handgrip exercise induced a different blood flow pattern, with negligible retrograde diastolic flow. Interestingly, this handgrip exercise flow pattern was not associated with the same magnitude of NO contribution to flow as that observed in the brachial artery during leg cycling exercise (11). This suggests that an oscillatory flow pattern may be important in the shear stress-mediated release of NO from the endothelium.

The precise reason for the increased retrograde flow in the brachial artery of the nonactive limb during cycling exercise is not fully understood. It is clear that systolic pressure-driven anterograde flow is immediately followed by retrograde flow during diastole, when the systolic driving force decreases and resistance in the forearm is presumably elevated. One likely explanation for the large retrograde blood flows that occurs in the nonactive upper limbs relates to increased peripheral vascular resistance by elevated sympathetic activity that occurs in inactive vessel beds during exercise.

The paralyzed legs of spinal cord-injured (SCI) subjects lack supraspinal sympathetic control. Accordingly, SCI subjects provide a unique opportunity to study exercise-induced blood flow changes in inactive areas lacking sympathetic innervation. Therefore, the aim of the present study was to assess acute changes in femoral artery blood flow and shear rate patterns during arm-crank exercise in 10 healthy controls and 10 SCI individuals. We hypothesized that sympathetic control importantly contributes to the retrograde blood flow and shear rate observed in the nonactive lower limbs during arm-crank exercise. We hypothesize that healthy controls, but not SCI subjects, would demonstrate an arm-crank exercise-induced increase in femoral artery retrograde blood flow and shear rate.

METHODS

Subjects

Ten male SCI subjects with a complete thoracic spinal cord lesion and 10 male healthy controls participated in the study (Table 1). All subjects had normal arm function, were otherwise healthy, and performed physical activity on a regular basis. No subject reported having been diagnosed with cardiovascular disease, diabetes, or insulin resistance or possessed cardiovascular risk factors such as hypercholesterolemia or hypertension. All SCI subjects had a complete

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sensory and motor thoracic spinal cord lesion [ASIA A (19)]. The presence of a complete thoracic lesion makes an intact supraspinal sympathetic innervation of the legs unlikely (20). In support of this, sweating was disturbed under the level of the lesion in all SCI subjects, indicating loss of sympathetic control below the lesion level. After a resting period of 25 min, baseline diameter and velocity of the femoral and brachial artery were assessed. Using a 5-mHz echo Doppler ultrasound device (SSA 270A; Toshiba), blood flow and vessel diameter were assessed by a well-trained sonographer. The femoral artery was measured 2 cm proximal to the bifurcation in the deep and superficial femoral artery of the right leg. The insolation angle was kept below 60° and in the middle of the vessel to accurately record velocity tracings.

After baseline measurements, subjects started exercise at 50% of their individual maximal arm-crank workload. Every 5 min, femoral artery diameter and velocity were recorded. In addition, mean arterial blood pressure was assessed one time every 5 min, manually at the ankle, taking the individual hydrostatic pressure into account. This is a reliable alternative for upper limb blood pressure measurements (4) while blood pressure assessment in the ankle can accurately detect changes in pressure during arm-crank exercise (17). Furthermore, oxygen uptake was examined continuously throughout the 25-min exercise bout to evaluate the relative intensity levels.

Data Analysis

Femoral artery diameter, flow, and shear rate. One investigator analyzed off-line recordings of arterial images and red blood cell velocities. Systolic (the largest) and diastolic (the smallest) vessel diameters were measured from three consecutive images and then averaged to calculate the mean diameter [$D_{\text{systolic}}$ + $D_{\text{diastolic}}$]. Furthermore, beat-to-beat red blood cell velocity was stored every 10 s for 2 min, resulting in 12 Doppler spectral waveforms that were manually traced off-line by an experienced investigator. These data from the Doppler spectrum waveforms were used to calculate the following blood velocities: 1) peak systolic anterograde blood velocity ($V_{\text{max}}$), defined as the highest velocity measured in the Doppler spectrum of a cardiac cycle, 2) peak retrograde velocity ($V_{\text{max}}$), defined as the lowest velocity in the Doppler spectrum of a cardiac cycle; and 3) mean blood velocity ($V_{\text{mean}}$), defined as the average velocity of the enveloping Doppler spectrum across the entire cardiac cycle. Mean inflow volume was calculated from the product of the arterial cross-sectional area and the $V_{\text{mean}}$ ($V_{\text{max}}$ = $(1/2 \times \pi \times D_{\text{max}}^2 \times V_{\text{mean}} \times 60)$. Peak anterograde and retrograde blood flows were also calculated (peak anterograde: $1/2 \times \pi \times D_{\text{max}}^2 \times V_{\text{max}}$; peak retrograde: $1/2 \times \pi \times D_{\text{max}}^2 \times V_{\text{min}}$). Vascular conductance was calculated as blood flow divided by mean arterial pressure (10). Mean wall shear rate ($s^{-1}$) was obtained from the calculation ($V_{\text{mean}}$ × 4)/$D_{\text{max}}$. Peak anterograde and retrograde wall shear rates were obtained from four times $V_{\text{peak}}$ and $V_{\text{min}}$ divided through the systolic or diastolic diameter, respectively.

Oxygen uptake. Oxygen uptake (in ml O$_2$·kg$^{-1}$·min$^{-1}$) during the 25-min exercise bout was determined and averaged over 30-s intervals by an automatic gas analyzer (Oxycon IV; Mijnhardt, Bunnik, The Netherlands). This included a dry gas meter and a paramagnetic O$_2$ and an infrared CO$_2$ analyzer and was calibrated daily with gas mixtures analyzed by the Scholander technique.

Statistics

Statistical analyses were performed using SPSS 14.0 (SPSS, Chicago, IL) software. All data are reported as means (SD), and statistical significance was assumed at $P < 0.05$. Repeated-measures ANOVA and post hoc paired $t$-tests with Bonferroni’s adjustment for multiple comparison were used to assess the impact of arm-crank exercise on blood flow and shear pattern (antero- and retrograde flows) in the femoral artery across the 25-min exercise bout. A two-way repeated-measures ANOVA was used to examine differences between groups and whether there was an interaction effect between groups and the effect of exercise on femoral artery blood flow and shear rate.
RESULTS

Baseline characteristics were not different between groups (Table 1). The workloads during the maximal arm-crank test and 25-min exercise bout were not different between groups. Average oxygen uptake during the 25-min exercise bout was similar between controls (18.0 ± 2.2 ml O₂·kg⁻¹·min⁻¹) and SCI (17.0 ± 3.9 ml O₂·kg⁻¹·min⁻¹, \( P = 0.51 \)). Mean, systolic, and diastolic arterial pressure did not differ between groups at rest, whereas exercise significantly increased mean, systolic, and diastolic blood pressure in controls, but not in SCI (Table 2).

Femoral Artery Blood Flow Responses During Arm-crank Exercise

Before exercise, controls demonstrated a significantly larger femoral artery blood flow (Fig. 1) and diameter than SCI. Arm-crank exercise did not change femoral artery diameter, whereas blood flow was increased in controls and SCI (Fig. 1B). Femoral artery peak anterograde blood flow increased, whereas blood flow was increased in controls and SCI (Fig. 1). Arm-crank exercise did not change femoral artery diameter, femoral artery blood flow (Fig. 1) and diameter than SCI. After correction for blood pressure changes during exercise by calculation of vascular conductance, neither group demonstrated a change in femoral artery vascular conductance during arm-crank exercise (Fig. 1C).

Femoral Artery Shear Rate Pattern During Arm-crank Exercise

At baseline, a significantly lower mean shear rate was present in SCI (13 ± 6) compared with controls (27 ± 6, \( t \)-test: \( P < 0.001 \)). Exercise resulted in a significant increase in mean shear rate in both groups. The exercise-induced change in mean shear rate was not different between controls and SCI (Fig. 2A).

To gain better insight into the exercise-induced changes in femoral artery shear rate pattern, we also expressed the peak anterograde and retrograde shear rates. Whereas SCI subjects exhibited lower mean shear, they demonstrated a significantly larger baseline peak anterograde shear rate than controls (41 ± 11 and 31 ± 8, respectively, \( t \)-test: \( P < 0.001 \)), whereas peak retrograde shear rates were not significantly different between both groups (−9 ± 3 and −11 ± 3, respectively, \( t \)-test: \( P = 0.30 \)). During arm-crank exercise, femoral artery anterograde and retrograde shear rate increased significantly in controls and in SCI. The increase in peak retrograde shear rate during arm-crank exercise induced in SCI subjects was significantly larger than in controls (Fig. 2C).

Table 2. Changes in mean arterial pressure during the arm-crank exercise protocol at regular intervals of 5 min in control and SCI subjects

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Controls (n = 10)</th>
<th>SCI (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>5</td>
</tr>
<tr>
<td>Systolic</td>
<td>140±14</td>
<td>159±22</td>
</tr>
<tr>
<td>Diastolic</td>
<td>70±7</td>
<td>100±25</td>
</tr>
<tr>
<td>MAP</td>
<td>95±9</td>
<td>120±23</td>
</tr>
<tr>
<td>Systolic</td>
<td>127±17</td>
<td>143±26</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73±19</td>
<td>80±14</td>
</tr>
<tr>
<td>MAP</td>
<td>91±17</td>
<td>101±17</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD; n, no. of subjects. MAP, mean arterial pressure. No differences were reported at baseline between controls and SCI regarding mean, systolic, and diastolic blood pressure (unpaired \( t \)-test). \( P \) value represents \( t \)-test between baseline and average blood pressure between 0 and 20 min (0-20 min).
This is the first study to examine femoral artery blood flow and shear rate responses to arm-crank exercise in either able-bodied controls or SCI subjects. The results indicate that arm-crank exercise induces a minimal increase in femoral mean artery blood flow, whereas peak anterograde and retrograde shear rates undergo marked changes. This finding is essentially a corollary of our previous report (11) in which we demonstrated that leg cycle ergometry induces a marked increase in diastolic retrograde flow in the inactive brachial artery. However, the present study is unique in that we examined healthy subjects and those without supraspinal sympathetic control. This enabled us to examine the impact of sympathetic control on flow changes in the inactive limbs. Interestingly, and in contrast with our hypothesis, SCI subjects demonstrated a similar change in the oscillatory pattern in the femoral artery as that observed in controls, that is, the increase in peak anterograde and retrograde shear rate during arm-crank exercise was similar in controls and SCI subjects. We were particularly surprised by the threefold increase in retrograde shear rate in SCI subjects, since we expected changes in retrograde flows to result from an increased SNS-mediated vascular tone in the legs during upper limb exercise. Because the SNS cannot be responsible for any increase in the retrograde part of the leg flow pattern in SCI subjects, other mechanisms may contribute to exercise-induced changes in the femoral artery shear rate pattern in SCI subjects.

In the femoral artery, controls demonstrated an ~50% increase in blood flow. This suggests that, during arm-crank exercise at 50% of the maximal capacity, blood flow in the femoral artery of the nonactive lower limbs only minimally increases from resting conditions. Historical studies established the tenet that blood flow to inactive vessel beds does not greatly increase during exercise such that, as a proportion of cardiac output, O2 transport is redistributed to active regions (2, 3, 16). The modest changes in femoral artery flow (49%) and conductance (23%) we observed concur with this schema in that they suggest the increase in cardiac output during arm-crank exercise is preferentially distributed to the active upper extremity musculature. More importantly, despite the modest changes in mean femoral artery blood flow and shear rate, we observed large exercise-induced changes in anterograde and retrograde shear rates. Peak anterograde shear rate increased ~70 and 60% in controls and SCI, whereas retrograde shear rate increased ~80 and 200%, respectively. This finding confirms previous experiments that examined inactive upper limb flow during leg exercise (10, 11). It also indicates that important information regarding the blood flow pattern is likely to be missed when mean blood flow or mean shear rates are presented without attention to the underlying pattern of change.

The importance of examining flow and shear rate patterns, rather than mean values only, is emphasized when comparing
controls with SCI subjects. While femoral artery resting mean blood flow and mean shear rate were 50–70% lower in SCI subjects than controls, baseline peak retrograde shear rate was comparable and peak anterograde shear rate was 30% higher in SCI than in controls. Anterograde peak shear rate is driven by cardiac output and systolic blood pressure as well as characteristics of the arterial wall. Because mean arterial pressures did not differ between groups, the larger peak anterograde shear rate in SCI may be explained by a lower arterial cross-sectional area and higher conduit artery stiffness, as previously demonstrated in the legs of SCI subjects (7).

During diastole, an exercise-induced increase in peak retrograde shear rate was observed in both groups. We hypothesized that increases in diastolic retrograde flow would reflect increases in sympathetic vasoconstrictor tone in the inactive lower limb during upper limb exercise. However, SCI subjects, who lack supraspinal sympathetic control in the lower limbs, also demonstrated an increase in retrograde flow pattern during exercise comparable to that observed in controls. This suggests a role for mechanisms other than supraspinal sympathetic control to explain the increase in retrograde shear rate in the nonactive limb of SCI subjects. Several possibilities exist, including an enhanced elastic rebound during diastole as a consequence of increased systolic pressure and anterograde velocity during exercise. Interestingly, SCI subjects demonstrate an increased arterial stiffness in the femoral artery (7), which may contribute to the changes in peak anterograde and retrograde shear rate observed in this study. An associated explanation relates to the possibility of increased myogenic responses during diastole following increases in systolic pressure with exercise. However, the myogenic response is suggested to occur over many seconds (25) and, therefore, may be too slow to explain the fluctuations in flow across the cardiac cycle.

Although the exercise-induced increase in retrograde peak shear rate we observed in SCI subjects implies that nonneural factors play a role in this group, we cannot rule out the possibility that the sympathetic nervous system (SNS) contributes to alterations in blood flow and shear rate in able-bodied subjects. It might be that different mechanisms are involved in blood flow and shear rate changes in SCI and able-bodied controls. Indeed, our laboratory recently reported that SCI subjects are able to increase leg vascular resistance (14) and maintain blood pressure (13) during upright tilt, a response that was originally thought to be regulated through the SNS. Taken together, our findings suggest that supraspinal sympathetic control is not obligatory for the changes in shear rate pattern during exercise in humans and that, in the absence of intact sympathetic innervation, redundant mechanisms contribute to vascular control.

Although the groups were well-matched for age, because of the extreme inactivity of the legs, a smaller femoral artery is present in SCI subjects. This smaller artery diameter importantly impacts blood flow and shear rate levels in SCI subjects. For example, in our study, we found femoral artery mean blood flow levels in SCI subjects that were only ~30% of that observed in controls. Consequently, also anterograde and retrograde flows were markedly lower in SCI. Nonetheless, because shear rate is regarded as the stimulus that transduces endothelium signals to remodeling and acute changes in vascular tone (26), we concentrated on shear rate rather than blood flow data in the present study. Although elevated baseline shear rate levels are commonly reported in the paralyzed legs of SCI subjects (5, 8, 9, 18, 22), we observed somewhat lower shear rate levels in the present study. Because a smaller artery in SCI is a common finding, the unexpected lower shear rate levels are likely the result of the lower blood flow in SCI subjects. The reasons for this are not clear but may relate to characteristics of the subjects or the procedures undertaken. Nonetheless, retrograde peak shear rates were similar between groups, whereas anterograde peak shear rates were 30% higher in SCI than in controls. Accordingly, the differences in mean femoral artery shear rate or blood flow do not impact the primary outcome of the study, that is, the examination of changes in femoral shear rate pattern during arm-crank exercise.

Clinical Relevance

The typical blood flow pattern that occurs in the brachial artery during cycle exercise, characterized by the marked increase in retrograde blood flow during diastole, is linked with a shear rate-mediated release of endothelium-derived NO (11, 12) that may contribute to training-induced improvements in brachial artery endothelial function as a function of lower limb training (11). Interestingly, the arm-crank exercise-induced changes in femoral artery flow pattern mimic the typical brachial artery oscillatory pattern during cycling. If the oscillatory pattern in the femoral artery is also linked with NO release, our observation may be of clinical relevance for SCI subjects or subjects who are restricted to upper limb activities to improve endothelial function in nonactive muscle beds. However, the impact of upper limb exercise on lower limb vascular health, especially in SCI or subjects restricted to upper limb exercise, requires further basic (mechanistic blockade) and applied (arm-crank training) studies to gain better insights into the potential clinical benefit for these subjects.

Limitations

A limitation of our study is related to the presentation of peak anterograde and retrograde values only, rather than those calculated from an area under the curve for retrograde and anterograde flow or shear. Our data therefore accurately describe the main characteristics of the shear rate pattern but not quantitative data. Another limitation of the present study is that we did not directly examine SNS activity to verify the exercise-induced increase in sympathetic activity in the legs of controls. However, the exercise bout was performed at 50% of the individual maximal work load, leading to an approximately fivefold increase in oxygen uptake. Previous studies demonstrated that much lower intensity levels than those used in the present study are associated with a marked increase in sympathetic nerve activity (15, 24). Therefore, we assume that our exercise protocol induced a significant increase in leg sympathetic nerve activity in controls. In addition, we performed the ankle blood pressure measurement in able-bodied subjects and SCI subjects. The potential differences in arterial stiffness (7) and endothelial function (8) between these groups might influence the validity of the ankle blood pressure measurement in SCI subjects. Finally, we were not able to examine EMG activity of the quadriceps during our protocol in all subjects. Additional experiments in three able-bodied subjects revealed
a modest change from baseline, which is unlikely to explain the main findings of our study, since we found no interaction effect between SCI (who have paralyzed legs) and controls regarding the effect of arm-cranking on femoral artery mean flow, conductance, or shear rate (Figs. 1–2).

In summary, we observed that, while arm-crank exercise results in minimal change in mean femoral artery blood flows, peak anterograde and retrograde shear rates demonstrate marked changes. A reproducible exercise-induced change in oscillatory shear rate pattern in the inactive regions was present in subjects with, and without, sympathetic innervation of the lower limbs. The large increase in retrograde shear rate that we observed in SCI subjects is interesting and results from an increase in leg peripheral resistance during the diastolic phase of the cardiac cycle. Because the SNS cannot be responsible for the change in the retrograde component of the oscillatory blood flow pattern in SCI subjects, other vasoconstrictor mechanisms likely contribute to exercise-induced changes in the femoral artery shear rate pattern during arm-crank exercise.

GRANTS

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