Influence of sympathetic vasoconstrictor tone on conduit artery retrograde and oscillatory shear: Effects of habitual aerobic exercise in middle-aged and older adults

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Abstract Retrograde and oscillatory shear can induce profound pro-atherogenic effects on endothelial cells, and increase with advancing age in peripheral conduit arteries. Habitual aerobic exercise ameliorates conduit artery retrograde and oscillatory shear in middle-aged and older adults; however, the mechanisms underlying the change in conduit artery shear rate patterns caused by habitual aerobic exercise remains unclear. This study investigated the role of sympathetic vasoconstrictor tone in the habitual aerobic exercise-induced change in conduit artery shear in middle-aged and older adults. Fifteen healthy middle-aged and older adults (aged 52-67 years; 4 men, 11 women) were divided into physically-active and sedentary control groups, based on reported exercise history. We measured brachial artery shear rate patterns at rest and during sympathetic nerve activity stimulation (via lower body negative pressure [LBNP] at -20 mmHg). At rest, the physically-active group showed smaller brachial artery retrograde and oscillatory shear compared to a sedentary control group ($p < 0.05$). The levels of brachial retrograde and oscillatory shear were elevated by the LBNP stimulation in the physically active group ($p < 0.05$), but not in the sedentary control group. Our results suggest that the attenuated basal sympathetic vasoconstrictor tone may contribute to the habitual aerobic exercise-induced decreases in conduit artery retrograde and oscillatory shear at rest in middle-aged and older adults.

Keywords : shear rate, aging, habitual aerobic exercise, sympathetic vasoconstrictor tone, atherosclerosis

Introduction

Hemodynamic shear stress is defined as the frictional force of blood on the arterial wall. Shear stress demonstrates a typical pattern (i.e., antegrade and retrograde shear) in conduit arteries. Elevation in retrograde and oscillatory shear may have pro-atherogenic effects¹⁻⁶. Aging causes increased retrograde shear and oscillatory shear in peripheral conduit arteries⁷⁻¹⁰. Meanwhile, a recent study reported that exercise-trained elderly individuals have lower retrograde and oscillatory shear compared to age-matched sedentary peers⁹. However, the mechanisms underlying the difference in conduit arteries shear rate patterns caused by habitual aerobic exercise remain unclear.

Conduit artery shear rate patterns are affected by downstream vascular resistance^{2,11,12}. Previous research has demonstrated that acute elevations in vascular resistance that occur via an increase in muscle sympathetic nerve

activity (MSNA) with lower body negative pressure (LBNP) are associated with an increase in conduit artery retrograde and oscillatory shear¹². Moreover, Casey et al. reported that α -adrenergic vasoconstriction of the downstream resistance vessels is a major contributor to age-related increases in conduit arteries retrograde and oscillatory shear at rest⁸. Because habitual aerobic exercise is effective in attenuating sympathetic nervous activity^{13,14}, it is possible that the attenuated sympathetic vasoconstrictor tone contributes to the habitual aerobic exercise-induced decrease in conduit artery retrograde and oscillatory shear in older adults.

With this information as background, the purpose of the present study was to determine the role of sympathetic vasoconstrictor tone in the effects of habitual aerobic exercise on conduit artery retrograde and oscillatory shear in middle-aged and older adults. We hypothesized that active middle-aged and older adults have low levels of conduit artery retrograde and oscillatory shear; and this exercise-induced benefit on shear rate patterns is asso-

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ciated with the attenuated sympathetic vasoconstrictor tone. To determine this hypothesis, in a cross-sectional study, we assessed brachial artery shear rate patterns in both resting and increased sympathetic nerve activity (via LBNP) conditions in middle-aged and older adults with and without aerobic exercise habits.

Patients and Methods

Subjects. A total of 15 healthy middle-aged and older individuals (aged 52–67 years; 4 men, 11 women) participated in the present study. All subjects were non-smokers and free of cardiovascular disease, as indicated by their medical history. None of the subjects were taking cardiovascular medications. All female subjects were postmenopausal and were not taking any form of hormone replacement therapy. The middle-aged and older adults consisted of two separate groups based on a self-reported measure of habitual physical activity. The two groups were defined as ‘sedentary control group’ (<3 days per week and <30 min exercise per day), and ‘physically-active group’ (≥ 3 days per week and ≥ 30 min moderate-to-vigorous intensity aerobic exercise per day)¹⁵⁾. The average times of aerobic exercise (i.e., walking, running, cycling, tennis and badminton) in the sedentary control group and physically-active group were 6.1 ± 5.1 min/day and 48.8 ± 20.2 min/day, respectively. This study was approved by the Ethical Committees of the Institute of Health and Sport Sciences of the University of Tsukuba (Approval number: 26–122). The study conformed to the principles outlined in the Helsinki Declaration, and all subjects were provided written informed consent prior to inclusion in the study.

Experimental design. All experiments, excluding the cycle exercise test (having a light meal before the exercise test), were performed in the morning after a 12-hour (h) overnight fast. Subjects abstained from alcohol and caffeine for at least 12 h and did not exercise for at least 24 h before beginning the experiment to avoid any potential acute effects of exercise. Measurements were obtained in a quiet, temperature-controlled room (24–26°C). Hemodynamics were collected in both resting and sympathetic stimulation (via LBNP) conditions. After the hemodynamic measurements, oxygen uptake at the ventilatory threshold ($\dot{V}O_{2VT}$) was measured during incremental cycle ergometer exercise.

Lower body negative pressure (LBNP). 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 crests. 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 mmHg. All variables were continuously recorded for 3 minutes while at the target LBNP pres-

sure (-20 mmHg). It is known that the application of low levels of LBNP (-20 mmHg) increases MSNA without concurrent changes in heart rate and arterial pressure¹⁶⁾. Moreover, this level of LBNP increases MSNA in older adults¹⁷⁾.

Measurements

Brachial artery properties

To examine brachial artery properties, the arm was extended and positioned at an angle of 80° from the torso. A 10-MHz multi-frequency linear array probe, attached to a high-resolution ultrasound machine (Logiq e, GE Healthcare, Tokyo, Japan), was then used to image the brachial artery in the distal one-third of the upper arm. Continuous Doppler velocity assessments were also obtained using the ultrasound and were collected using the lowest possible insonation angle (always 60°). Images of the brachial artery and associated velocity waveform from the Doppler ultrasound machine were stored in a computer at a frequency of 30 Hz¹⁸⁾, using a frame grabber (DVI2USB 3.0, Epiphan, USA), for offline analysis.

Artery diameter and time-averaged mean blood velocity were calculated using image analysis software (S-14081, Takei Kiki Kogyo, Niigata, Japan). Calculations were performed during a 30 sec recording of brachial artery diameter and velocity to calculate antegrade and retrograde shear rate. Shear rate was defined as $4 \cdot \text{velocity} / \text{diameter}$. The 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: $|\text{retrograde shear}| / (|\text{antegrade shear}| + |\text{retrograde shear}|)$ blood flow was defined as $\pi \cdot (\text{diameter} / 2)^2 \cdot \text{velocity} \cdot 60^{7-9)}$. The day-to-day coefficient of variations for retrograde shear rate under resting and LBNP conditions were 7.6% and 9.4%.

Aerobic capacity

$\dot{V}O_{2VT}$ was measured during incremental cycle ergometer exercise using online computer-assisted circuit spirometry (AE300S; Minato Medical Science, Osaka, Japan). Before and after the intervention, all subjects underwent an incremental cycle exercise test (2 min at 20 watts [W], followed by 10-W increases every 1 min) until they felt exhausted or reached 85% of their age-predicted maximal heart rate. Each individual $\dot{V}O_{2VT}$ was calculated using regression analysis of the slopes of CO_2 production, O_2 uptake, and the minute ventilation (MV) plot¹⁹⁾.

Statistical analyses

Shear profile variables were compared via repeated measures ANOVA to detect differences between groups and across conditions. Appropriate post hoc analysis determined where statistical differences occurred. Unpaired Student's t-tests were used to evaluate differences between the physically active and sedentary control groups. All data are reported as means $\pm$ SD. Statistical significance was set *a priori* at $p < 0.05$ for all comparisons.

Results

Subject characteristics are summarized in Table 1. No significant differences in the proportion of women, age, height, weight, body mass index, systolic blood pressure and diastolic blood pressure were observed between the two groups. The physically-active subjects demonstrated a greater $\dot{V}O_{2VT}$ than their sedentary control counterparts ($p < 0.05$).

Heart rate and brachial artery properties are summarized in Table 2. No significant differences in the heart rate, brachial artery diameters, mean velocity, antegrade velocity, retrograde velocity, mean shear rate, antegrade

shear rate were observed between the groups in resting condition. Additionally, the physically-active group presented a greater mean blood flow and antegrade blood flow compared with the sedentary control group in resting condition. In the LBNP condition, there were no significant changes in heart rate and brachial artery diameters in either of the groups. In the physically-active group, mean velocity, antegrade velocity, retrograde velocity, mean blood flow, antegrade blood flow, retrograde blood flow, mean shear rate, and antegrade shear rate changed during LBNP from resting condition. In contrast, the sedentary control group demonstrated an unchanged mean velocity, antegrade velocity, retrograde velocity, mean blood

Table 1. Subject characteristics

Characteristics of selected subjects

Variables	Sedentary control (n = 8)			Physically-active (n = 7)		
women, n	6			5		
Age, yr	60.4	±	4.2	61.3	±	6.0
Height, cm	162.7	±	8.0	163.2	±	3.4
Body mass, kg	61.5	±	11.2	59.9	±	5.0
Body mass index, kg/m ²	23.1	±	2.9	22.5	±	1.2
Systolic blood pressure, mmHg	120	±	17	114	±	13
Diastolic blood pressure, mmHg	72	±	10	71	±	8
$\dot{V}O_{2VT}$, ml · min ⁻¹ · kg ⁻¹	11.8	±	1.7	17.6	±	3.4*

Data are expressed as means ± SD. * $p < 0.05$ vs. Sedentary control group. $\dot{V}O_{2VT}$ indicates oxygen uptake at the ventilatory threshold.

Table 2. Heart rate and brachial artery properties at rest and lower body negative pressure (LBNP) conditions

Variables	Sedentary control		Physically-active	
	Rest	LBNP	Rest	LBNP
Heart rate, bpm	55 ± 4	54 ± 4	55 ± 4	56 ± 4
Brachial artery diameter, cm	0.37 ± 0.05	0.37 ± 0.05	0.42 ± 0.04	0.42 ± 0.04
Mean velocity, cm s ⁻¹	6.2 ± 2.6	6.0 ± 2.9	9.9 ± 3.2	5.5 ± 1.7†
Antegrade velocity, cm s ⁻¹	6.7 ± 2.4	6.5 ± 2.6	10.1 ± 3.1	6.5 ± 1.4†
Retrograde velocity, cm s ⁻¹	-0.5 ± 0.3	-0.5 ± 0.4	-0.2 ± 0.2	-1.0 ± 0.6†
Mean blood flow, ml min ⁻¹	40.8 ± 21.2	39.9 ± 23.2	79.8 ± 19.7*	46.1 ± 16.3†
Antegrade blood flow, ml min ⁻¹	44.1 ± 21.3	43.5 ± 22.5	81.6 ± 19.3*	53.9 ± 14.1†
Retrograde blood flow, ml min ⁻¹	-3.3 ± 2.5	-3.6 ± 3.0	-1.8 ± 2.0	-7.7 ± 4.9†
Mean shear rate, s ⁻¹	67.9 ± 29.0	65.3 ± 30.1	96.1 ± 36.3	53.2 ± 17.1†
Antegrade shear rate, s ⁻¹	73.9 ± 26.8	71.1 ± 27.0	98.1 ± 35.5	62.6 ± 15.0†

Data are expressed as means ± SD. * $p < 0.05$ vs. Sedentary control group. † $p < 0.05$ vs. Rest.

flow, antegrade blood flow, retrograde blood flow, mean shear rate, and antegrade shear rate in the LBNP condition. As shown in Fig. 1, the physically-active group presented less retrograde (-2.0 ± 2.0 vs. -5.2 ± 2.8 , $p < 0.05$) and oscillatory shear (0.02 ± 0.02 vs. 0.08 ± 0.05 , $p < 0.05$) compared to the sedentary control group in resting condition. Sympathetic activation via LBNP was found to increase the magnitude of the retrograde shear rate (-2.0 ± 2.0 to -9.3 ± 6.3 , $p < 0.05$) and oscillatory shear (0.02 ± 0.02 to 0.13 ± 0.08 , $p < 0.05$) in the physically-active group. On the contrary, no significant change in retrograde (-5.2 ± 2.8 to -5.8 ± 3.9 , not significant [NS]) and oscillatory shear (0.08 ± 0.05 to 0.09 ± 0.07 , [NS]) was observed in the sedentary control group in the LBNP condition. Among all subjects, there was no correlation between physical activity and brachial retrograde and oscillatory shear in the LBNP condition (NS).

Discussion

The major findings of the present study are as follows. Physically active middle-aged and older adults demonstrate significantly lower retrograde and oscillatory shear

in the brachial artery, compared to their age-matched sedentary control counterparts. Moreover, sympathetic activation increased brachial retrograde and oscillatory shear in the physically-active group, but not in the sedentary control group. Therefore, the attenuated sympathetic vasoconstrictor tone may contribute to the habitual aerobic exercise-induced decreases in conduit artery retrograde and oscillatory shear at rest in middle-aged and older adults.

In the present study, the physically active middle-aged and older adults exhibited lower retrograde and oscillatory shear in the brachial artery compared to the sedentary individuals. Lower brachial retrograde and oscillatory shear were consistent with results of previous interventional studies^{20,21)} demonstrating that short-term aerobic exercise training reduces brachial artery retrograde shear. On the other hand, Casey et al.⁹⁾ reported that endurance exercise-trained older adults have lower retrograde and oscillatory shear in the common femoral artery; whereas they could not observe significant differences in the brachial artery between the endurance-trained individuals and their sedentary counterparts, though the endurance-trained had relatively lower retrograde and oscillatory shear. That might be due to the three-group comparisons that included young individuals. These results suggest a possibility that even in middle-aged and elderly populations, the deteriorated brachial artery shear rate patterns could be restored by regular aerobic exercise. Our findings advance the understanding of the effect of habitual aerobic exercise on the conduit artery shear profile in middle-aged and older adults.

The underpinning mechanisms responsible for lower conduit artery retrograde and oscillatory shear in physically-active elderly individuals had been unclear. A number of studies have provided evidence that the conduit artery shear pattern is affected by downstream vasoconstrictor tone^{2,7,8,11)}. Furthermore, the previous works in animal models has led to reports that chronic exercise training attenuated α -adrenergic vasoconstriction in resistance arterioles through upregulation of the NOS-signalling pathway¹⁴⁾. Accordingly, we examined whether sympathetic nervous activity was associated with favorable retrograde and oscillatory shear caused by regular endurance training. Sympathetic activation via LBNP increased brachial retrograde and oscillatory shear in the physically-active group, but not the sedentary control group. In the sedentary control group, who had relatively higher basal sympathetic vasoconstrictor tone, LBNP stimulation might not have induced a further increase in forearm vascular constrictor tone. To the contrary, in the physically-active group, the majority of brachial artery shear pattern responses to LBNP were significantly increased. In the physically-active group, relatively lower sympathetic vasoconstrictor tone in the downstream resistance vasculature at rest might be augmented with LBNP stimulation. Collectively, the various responses of conduit

Fig. 1 Brachial artery shear rate patterns [retrograde shear rate (A), oscillatory shear index (B)] at rest (with no stimulus) and sympathetic stimulation conditions (via lower body negative pressure; LBNP) in middle-aged and older individuals. Data are reported as means $\pm$ SD. * $p < 0.05$ vs. Sedentary control group. † $p < 0.05$ vs. Rest.

artery retrograde and oscillatory shear at rest to LBNP stimulation might be attributed to the difference in basal sympathetic vasoconstrictor tone between sedentary and physically-active middle-aged and elderly adults.

Experimental considerations. A few methodological considerations should be mentioned. First, our current study included a large proportion of women and a relatively small sample size. Since older women traditionally show a relatively stronger relationship between MSNA and peripheral vascular resistance compared to young and age-matched older men^{22,23}, it is plausible that gender-related effects may have affected conduit artery shear pattern responses to LBNP. Such features of the study sample might also explain the nonsignificant correlation between physical activity and brachial artery shear rate patterns. To generalize the findings of this study, further studies should be warranted with larger sample sizes and different populations, especially with older men. Second, we did not directly assess MSNA and forearm vascular resistance in resting and LBNP conditions. Therefore, we were unable to quantify the magnitude of sympathetic activation and vasoconstrictor tone. However, a previous study demonstrated that low levels of LBNP (-20 mm Hg) have consistently been shown to be effective in increasing MSNA in older adults¹⁷. Moreover, Davy and colleagues demonstrated that progressive increases in MSNA via graded LBNP are associated with a progressive increase in forearm vascular resistance in older adults¹⁷. Third, a previous study reported that conduit artery retrograde flow is associated with arterial stiffness and endothelial function²⁴. However, we did not look at these assessments. Further studies are needed to investigate the effects of habitual aerobic exercise on conduit artery retrograde and oscillatory shear with vascular function. Finally, in our current study, the physically-active group presented a greater mean blood flow compared to the sedentary control group in resting condition. In contrast, some previous studies reported no change in basal upper-limb mean blood flow from habitual aerobic exercise^{9,25,26}. The reason for the discrepancy between these studies is not entirely clear, but has been attributed to upper-limb exercise. Because of the cross-sectional approach used in our study, we could not control the specific type of chronic exercise subjects participated in. A few subjects performed upper limb exercise (i.e., tennis, badminton). Size and blood flow volume of the upper-limb arteries are enhanced by corresponding limb exercise training²⁷⁻²⁹. Therefore, it is possible that the basal hemodynamics in the current study were influenced by the upper-limb exercise habits. However, it has been reported that limb-specific exercise training does not affect sympathetic vasoconstriction³⁰. Hence, these limitations do not detract from the present study.

Conclusion

In conclusion, the present study demonstrated that physically active middle-aged and older adults demonstrate significantly lower retrograde and oscillatory shear in the brachial artery, compared to sedentary control age-matched participants at rest. Moreover, in the study, sympathetic activation increased brachial retrograde and oscillatory shear in the physically-active participants, but not in the sedentary control participants. Therefore, the attenuated sympathetic vasoconstrictor tone may contribute to the habitual aerobic exercise-induced decrease in conduit artery retrograde and oscillatory shear at rest in middle-aged and older adults.

Conflict of Interests

The authors declare that they have no conflict of interests.

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