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Characterization of the brachial artery shear stress following walking exercise

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Abstract: Habitual exercise provides repeated episodes of elevated vascular shear stress (SS), which may be a mechanism for repair of endothelial dysfunction in disease. Our aim was to determine the brachial artery SS during the 3–hour period following single bouts of low, moderate, and high-intensity walking exercise. In a randomized crossover design, 14 men walked for 45 minutes on a treadmill at 25%, 50% and 75% of VO_{2peak} separated by 2–7 days. Using Doppler ultrasonography, brachial artery SS was assessed immediately after exercise and then hourly for 3 hours. High-intensity walking elicited greater ($p < 0.05$) post-exercise SS compared with low and moderate intensity. In addition, a 3 × 4 (intensity × time) ANOVA indicated an absence of interaction ($p = 0.369$) and a decline in post-exercise SS over time ($p < 0.0001$) which was abolished after 2 hours. Thus, we found that brachial artery SS is greatest following high-intensity walking and that the rate of decline in SS is similar across all walking intensities.

Key words: Doppler ultrasonography; endothelial function; exercise intensity

Introduction

The impairment of endothelial function is the primary etiology of atherosclerotic cardiovascular disease,[1] the leading cause of morbidity and mortality in Western society.[2] Habitual exercise is among the strategies found to effectively repair a dysfunctional endothelium.[3–11]

A number of animal and human studies have been conducted to elucidate the biological mechanism by which habitual exercise repairs endothelial dysfunction.[12–14] From these studies, it is postulated that the primary stimulus triggering vascular remodeling may originate from the repeated hyperemic bouts associated with exercise.[12–14] Blood flow exerts a frictional force on the endothelial surface of the vessel lumen known as vascular shear stress. Recurring episodes of increased laminar shear stress cause an up-regulation of endothelial nitric oxide synthase (eNOS) mRNA and protein, permitting the endothelial cell to produce larger amounts of nitric oxide,[15,16] thus leading to enhanced vascular function. The biological pathway linking vascular shear stress and increased eNOS transcription and translation has been described elsewhere.[17]

Given that vascular shear stress is considered the initial signaling mechanism of exercise-induced repair of endothelial function,[12–14] an understanding of the nature of this stimulus under physiological conditions becomes imperative. A plethora of literature exists describing the kinetics of blood flow and shear stress during exercise.[18–22] These studies typically utilize the handgrip exercise model and measurements of blood flow and shear stress are performed at the brachial artery. However, there are a limited number of studies assessing the magnitude of blood flow or shear stress occurring at the brachial artery in response to leg (cycle-ergometer) exercise [23,24] and no studies have used whole-body (walking) exercise. In addition, the consideration of shear stress during the recovery from exercise (post-exercise) as a component of the overall exercise-mediated shear stimulus has been neglected. Characterization of the brachial artery shear stress following walking exercise seems appropriate for three main reasons. First, the brachial artery coincides with the location most suitable for non-invasive measurement of endothelial function;[25]

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thus, it is logical that the stimulus (shear stress) is measured at the same region. Second, walking is the most common form of physical activity and a mode of exercise training that effectively enhances endothelial function.[7,26] Third, shear stress occurring during recovery from exercise may contribute to the overall shear stimulus generated by the exercise bout, and thus it deserves attention.

Hence, the aim of the present study was to determine the brachial artery shear stress during the 3–hour period following single bouts of low, moderate, and high-intensity walking exercise. It was hypothesized that: (1) walking at the high intensity would elicit the greatest magnitude of shear stress, as represented by the area under the curve (AUC), followed by moderate and low-intensity walking; and (2) the rate of decline in shear stress would be similar across exercise intensities.

Methods

Experimental design

The post-exercise shear stress concept was identified after further analysis of data from a study that was designed to assess flow-mediated dilation for 3 hours following acute exercise at low, moderate, and high intensity. A within-subjects experimental design with three treatments, each separated by 2–7 days, was given to 14 men in a randomized order. Treatments consisted of walking exercise sessions of low, moderate, and high intensity. For each treatment, individuals were instructed to report to the laboratory at 7:30 am having (1) fasted for 12 hours, (2) abstained from exercise for 24 hours, and (3) abstained from caffeine and tobacco for 12 hours. Brachial artery shear stress was assessed immediately following the cessation of exercise and then every hour for 3 hours thereafter. The individuals were asked to remain seated in the laboratory between measurements. All procedures were approved by Indiana University's Committee for the Protection of Human Subjects. Written informed consent was obtained from each individual prior to participation in the study.

Participants

Fourteen men (aged 46–68 years) participated in this investigation. Individuals were excluded if they: (1) had any known cardiovascular, pulmonary or metabolic diseases, (2) had absolute contraindication to exercise testing as established by the American College of Sports Medicine,[27] and (3) were on any medications that influence arterial compliance.

Study procedures

The procedures of the study included risk stratification and screening; performance of a graded maximal exercise test; and completion of the three walking exercise sessions with subsequent assessment of brachial artery shear stress.

Risk stratification and screening

To determine the individual's risk stratification for exercise and eligibility for the study, each participant completed a medical history/health habits questionnaire and underwent measurements of height, weight, and resting blood pressure. In addition, a fasting venous blood draw was performed to obtain total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and blood glucose.

Graded maximal exercise test

A graded exercise test (VO_{2peak}) was performed to determine the individualized target intensity for each of the three exercise sessions. Briefly, the participants walked at a constant comfortable speed on a motor-driven treadmill with the grade increasing 2.5% every 2 minutes until volitional fatigue. Expired gases were collected into a mixing chamber through a unidirectional flow mouthpiece and analyzed using a Sensor Medics 2900 Metabolic Cart (Sensor Medics, Yorba Linda, CA, USA). To confirm that maximal effort had been achieved, objective and subjective criteria were used as described by the American College of Sports Medicine.[27]

Exercise treatments

Exercise treatments consisted of 45–minute continuous sessions of treadmill walking at a low (25% VO_{2peak}), moderate (50% VO_{2peak}), and high (75% VO_{2peak}) intensity. Each exercise treatment was separated by 2–7 days. Oxygen uptake (VO_2) was measured via a Sensor Medics 2900 metabolic cart (Sensor Medics) between the 5th and 10th minute of each exercise treatment to confirm the appropriate exercise intensity. The work rate was adjusted if the VO_2 was not within ± 5% of the target walking intensity. Following the adjustment (if necessary), other gas collections were made throughout the exercise period to ensure that the target exercise intensity was maintained. Heart rate (EKG), blood pressure (auscultation), and rating of perceived exertion (using the Borg Scale of 6–20)[28] were measured every 5 minutes throughout each exercise session.

Brachial artery shear stress

Shear stress was assessed at the brachial artery immediately following the cessation of exercise

and then every hour for 3 hours thereafter. Prior to each assessment (excluding the immediate measurement), participants lay supine for a 20–minute acclimation phase in a dark, climate-controlled room (22–24°C), with their right arm extended out laterally. The brachial artery was imaged longitudinally by a 2D high-resolution Sonoace Pico ultrasound system (Universal Medical Systems, Bedford Hills, NY, USA) using a 7.0-MHz linear transducer placed 2–10 cm above the antecubital fossa. Once a clear image was obtained, the transducer was placed in a stabilized holder and the position was marked on the skin to ensure the same placement for all measurements. Following the 20–minute acclimation period, brachial artery diameter and blood velocity were captured for 10 cardiac cycles. Blood velocity was measured using pulse Doppler with the Doppler flow signal corrected at an insonation angle of 70°. Measurements were performed with the sample volume gate (1.5 mm) placed in mid-artery. EKG gaiting was utilized to capture end-diastolic arterial diameters triggered by the QRS complex. Using the Vascular Analysis Integrative System (Medical Imaging Applications, Coralville, IA, USA), all measurements were performed by the same investigator who was blinded to the treatment condition. Reproducibility of our measurements has been reported previously.[29] Data were reported as averages for each 10 cardiac cycle. Vascular shear stress (dynes/cm^2) was then calculated using the equation $4 \times \mu \times MBV/D$, where μ is the blood viscosity (assumed as 4.0 cp), MBV is the mean blood velocity, and D is the mean diameter.[24,30] For each treatment condition, the magnitude of the 3–hour post-exercise shear stress was determined by calculating the AUC (arbitrary units) and summing the areas of the successive trapezoids.

Statistical analysis

Descriptive statistics were used to summarize the demographic characteristics of the participants. A one-way repeated measures ANOVA was utilized to compare the post-exercise shear stress AUC among the walking intensities. In addition, to compare the rate of decline in post-exercise shear-stress among intensities, a 3 × 4 (intensity × time) repeated measures ANOVA was performed. A 3 × 4 (intensity × time) repeated measures ANOVA was also employed to compare arterial diameters and blood velocities across conditions. When a significant *F*-ratio was found, Tukey's HSD test was used to detect differences. All data are presented as mean × standard error of the mean (SEM). For all statistical tests, the alpha level was set at 0.05. Statistical analyses were performed with SPSS v.14.0 (SPSS, Inc. Chicago, IL, USA).

Results

Demographic information of the participants is summarized in Table 1. Table 2 displays the physiological responses to the low, moderate, and high-intensity exercise sessions. All of the individuals reached and maintained the target walking intensity and none exhibited a cardiac drift.

One-way ANOVA exhibited statistical differences in post-exercise shear stress AUC among the walking intensities ($F_{(2,26)} = 4.35$; $p = 0.023$). As illustrated in Figure 1, walking at high intensity elicited greater ($p < 0.05$) post-exercise shear stress compared with low and moderate intensity, whereas no statistical differences were found between low and moderate intensity ($p > 0.05$). In addition, as presented in Figure 2, the 3 × 4 (intensity × time) ANOVA indicated an absence of interaction ($F_{(6,78)} = 1.10$; $p = 0.369$), and the presence of a main effect of walking intensity ($F_{(2,26)} = 4.78$; $p = 0.017$) and time ($F_{(3,39)} = 57.29$; $p < 0.0001$). When collapsing across walking intensities, Tukey's HSD test revealed pairwise differences among all times points except between hours 2 and 3. In addition, Table 3 displays all brachial diameter and blood velocity values following walking exercise of different intensities.

Discussion

The aim of the present study was to determine the brachial artery shear stress during the 3–hour period following single bouts of low, moderate, and high-intensity walking exercise. As hypothesized, we found that walking at high intensity elicited the greatest magnitude of shear stress, and that the

Table 1 Demographic characteristics of the individuals

Variable	Value
n	14
Age, years	58.6 ± 2.1
Height, cm	175.4 ± 1.2
Weight, kg	87.9 ± 2.5
Body mass index, kg/m^2	28.5 ± 0.7
Resting systolic blood pressure, mmHg	116.6 ± 2.9
Resting diastolic blood pressure, mmHg	76.4 ± 2.1
VO_{2peak}, ml/kg per min	32.8 ± 1.2
Reported physical activity[a], days/week	2.4 ± 0.6
Total cholesterol, mg/dl	195.2 ± 10.4
HDL cholesterol, mg/dl	49.4 ± 3.9
LDL cholesterol, mg/dl	117.0 ± 9.4
Triglycerides, mg/dl	144.3 ± 18.2
Fasting glucose, mg/dl	92.9 ± 1.6

Values are mean ± SEM.
[a]Aerobic physical activity of moderate intensity for 30 minutes or more.

Table 2 Physiological responses to walking exercise

Variable	Low intensity	Moderate intensity	High intensity
	(25% VO_{2peak})	(50% VO_{2peak})	(75% VO_{2peak})
Heart rate, bpm	79.9 ± 2.6	107.0 ± 2.7	139.0 ± 2.8
Systolic blood pressure, mmHg	124.3 ± 3.8	138.2 ± 4.6	163.3 ± 5.6
Diastolic blood pressure, mmHg	76.6 ± 3.0	72.5 ± 2.2	72.3 ± 2.8
Rating of perceived exertion	7.8 ± 0.2	11.5 ± 0.4	14.0 ± 0.4
VO_2, ml/kg per min	8.5 ± 0.2	16.5 ± 0.7	24.8 ± 1.0
VO_2, % peak	25.9 ± 0.4	50.2 ± 0.3	75.5 ± 0.6

Values are mean ± SEM.

rate of decline in shear stress was similar across walking intensities. Unexpectedly, we found a non-statistical difference in post-exercise shear stress between moderate and low-intensity walking. As anticipated, vasodilation and blood velocity were greatest following high-intensity walking exercise and arterial diameters and velocities declined throughout the recovery period.

Our findings suggest that the brachial artery continues to be exposed to increases in shear stress during the recovery from walking exercise and that improvement of endothelial function previously observed in training studies may not only be due to the elevated shear stress occurring during exercise[24] but also to the alteration during the recovery. Given that the exercise recovery phase may be longer than the actual duration of exercise, further research is needed to determine the relative contribution of recovery shear stress in relation to the shear stress generated during exercise.

The exercise intensity-dependent shear stress observed in our study is similar to that reported by Tanaka and colleagues.[24] They assessed brachial artery shear stress via Doppler ultrasonography during graded (to max) cycle-ergometry in a group of eight healthy women. They found that changes in shear stress, relative to a resting baseline, occurred after moderate intensities (> 50% of the maximal exercise capacity) were reached, and continued to increase to maximal work. Our findings are consistent with theirs in that the highest post-exercise shear stress was also associated with high-intensity exercise. In addition, our study demonstrated that brachial artery shear stress does not differ between low and moderate-intensity walking, which is also in accordance with the findings of Tanaka and colleagues.[24] In view of these findings, it is logical to anticipate that exercise training at high intensity would elicit the greatest enhancement in brachial artery endothelial function because shear stress is highest. The findings of Goto *et al.*,[31] however, are in contrast to this premise. They found that in healthy young men exercise training at moderate

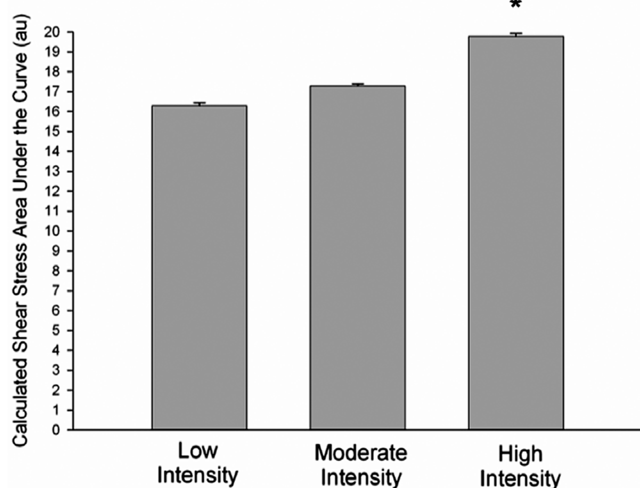

Figure 1 Post-exercise shear stress (area under the curve) among different walking intensities (mean ± SEM). *Significantly different ($p < 0.05$) from low and moderate intensity.

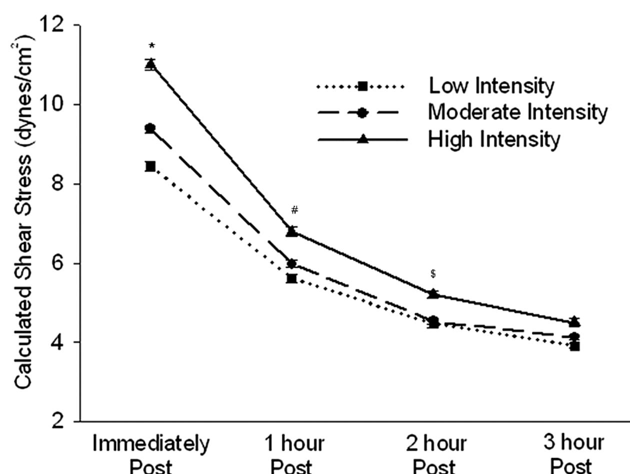

Figure 2 Rate of decline in shear stress following walking exercise of different intensities (mean ± SEM). *Significantly different from 1 hour post, 2 hours post, and 3 hours post collapsing across intensities; #significantly different from immediately post, 2 hours post, and 3 hours post collapsing across intensities; $significantly different from immediately post and 1 hour post collapsing across intensities. All $p < 0.05$.

Table 3 Brachial artery diameter and blood velocity values following walking exercise of different intensities

		Time post-exercise			
		Immediately	1 h	2 h	3 h
Artery diameter (mm)	Low intensity	4.16 ± 0.12[a]	4.10 ± 0.12	4.14 ± 0.12	4.06 ± 0.12
	Moderate intensity	4.11 ± 0.11	4.13 ± 0.11	4.07 ± 0.11	4.07 ± 0.11
	High intensity	4.32 ± 0.13[b,c]	4.26 ± 0.13[d]	4.14 ± 0.12	4.19 ± 0.12
Blood velocity (cm/s)	Low intensity	22.01 ± 2.47[e]	14.83 ± 2.11	11.71 ± 1.39	9.98 ± 0.69
	Moderate intensity	23.98 ± 1.40[e]	15.59 ± 1.47	11.60 ± 0.84	10.51 ± 0.54
	High intensity	29.60 ± 2.78[b,e]	18.20 ± 2.03[f]	13.60 ± 1.30	11.66 ± 1.21

Values are mean ± SEM.
[a]Significantly different from 3 h; [b]significantly different from low and moderate intensity; [c]significantly different from 2 h and 3 h; [d]significantly different from low intensity; [e]significantly different from 1 h, 2 h, and 3 h; [f]significantly different from 3 h.
All $p < 0.05$.

intensity (50% VO_{2max}) produced improvements in endothelial function, whereas low (25% VO_2max) and high (75% VO_{2max}) intensity exhibited no change. What can explain this unexpected disassociation between high-intensity exercise and enhancement of endothelial function? Acute and long-term high-intensity exercise has been shown to provoke an overproduction of reactive oxygen species[32] leading to an imbalance between pro-oxidants and antioxidant forces, also known as oxidative stress.[33,34] Oxidative stress is a physiological state postulated to be the major contributor to endothelial dysfunction.[35] It is possible that with high-intensity exercise, the induced oxidative stress negates the positive effect of shear stress on endothelial function. Indeed, Goto *et al.*[31] found that exercise training at high intensity, but not at moderate or low intensity, increased oxidative stress. In addition, it is also possible that high-intensity exercise may elicit an excessive magnitude of blood flow leading to a non-laminar shear stress, which has been shown not to enhance endothelial function.[17]

A limitation to this study is the utilization of Doppler ultrasonography to calculate shear stress. The true measurement of vascular shear stress in vivo is extremely complicated due to the pulsatility of the flow and the necessity for velocity and viscosity measurements in close proximity to the vessel wall. Estimation of shear stress, however, is possible in conduit arteries as the blood flow within these vessels is generally laminar and unidirectional.[25] Calculation of shear stress (also referred to as shear rate) has been extensively utilized in human research because of the non-invasive nature of the measurement.[30,36–40] The lack of assessment for blood lactate or other vasoactive substances can be considered another limitation to the study. It is possible that changes in shear stress at the highest work load may be a reflection of increased blood lactate levels or other factors associated with high-intensity exercise. Another limitation to this study is the potential influence of serial measurements of flow-mediated dilation (performed as part of the main investigation) on basal arterial diameter and blood velocity; however, our laboratory has demonstrated that repetitive flow-mediated dilation measurements (30 minutes apart) do not affect subsequent measures of basal arterial diameter, blood velocity, or flow-mediated dilation.[29]

In conclusion, we found that brachial artery shear stress is greatest following high-intensity walking with no statistical differences between low and moderate-intensity walking. In addition, we showed that the rate of decline in shear stress is similar across walking intensities. When considering the scientific evidence that exercise training at high intensity does not improve endothelial function, our findings may be of significance. We support the view that mechanisms other than vascular shear stress may be playing an important role in modulating endothelial function. Further research is also warranted to determine the relative contribution of recovery shear stress in relation to the shear stress generated during exercise.

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