Exercise-mediated changes in conduit artery wall thickness in humans: role of shear stress

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EXERCISE TRAINING is a well-established and potent physiological stimulus that reduces primary (30, 33, 40) and secondary cardiovascular events (19, 32). The cardioprotective effects of exercise training may, at least in part, be explained by the direct effects of repeated exercise bouts on the vasculature (20). Indeed, exercise training improves vascular function (42), which relates to decreased cardiovascular risk and attenuation of atherogenic processes (7, 8, 15, 18). In addition, exercise training decreases artery wall thickness (9, 16, 41), which may be associated with a decreased progression of atherosclerosis (25, 26).

The mechanisms associated with the effects of exercise training on artery (wall) remodeling may be related to local and/or systemic factors (23). Animal studies have demonstrated the importance of shear stress in modulating arterial size (21, 46) and also wall remodeling (6, 46). Human studies also demonstrate the importance of episodic increases in local shear stress to increase conduit artery diameter (45), and observational data suggest an inverse correlation between resting shear stress and carotid artery wall thickness (13). However, the role of shear stress in modulating conduit artery wall thickness has not been directly addressed experimentally in humans.

In the present study, we used a within-subjects design, involving simultaneous 8 wk of handgrip training of identical exercise intensity and duration in both arms. During these supervised exercise bouts (30 min, 4 times/wk), blood flow and shear stress were manipulated in one arm using cuff inflation around the forearm, which decreased shear stress during exercise in that limb. We examined bilateral brachial artery wall remodeling at two weekly intervals over the 8-wk training period using high-resolution ultrasound. We hypothesized that the manipulation of exercise-induced shear stress would induce differences between the limbs in artery wall thickness.

METHODS

Subjects

Seventeen men were recruited to examine the acute effects of handgrip exercise in the noncuffed and cuffed arms on brachial artery blood flow and shear pattern (n = 10, 28 ± 7 yr) or blood pressure (n = 7, 23 ± 3 yr). Another eleven recreationally active men were recruited and allocated to an 8-wk exercise training intervention (Table 1). All subjects were young and healthy; none had been diagnosed with cardiovascular disease, diabetes, insulin resistance, or cardiovascular risk factors such as hypercholesterolemia or hypertension. Subjects who smoked or were on medications of any type were excluded. The study procedures were approved by the Ethics Committee of Liverpool John Moores University and adhered to the Declaration of Helsinki. Informed consent was gained from all participants before the experimental procedures.

Experimental Design

Initially, we examined the acute effects of a 30-min handgrip exercise protocol. After measurement of preexercise baseline blood flow and shear pattern in both arms, we examined blood flow and shear patterns during bilateral handgrip exercise to establish that distinct shear stress stimuli existed in the cuffed versus noncuffed arms. In another group of subjects, we examined blood pressure during the exercise bout in the cuffed versus noncuffed arms.

To examine the impact of 8 wk of handgrip training, subjects reported to the laboratory for an initial assessment of anthropometric and vascular measurements. An assessment of wall thickness and lumen diameter were taken at the beginning of the training program and then every 2 wk until the end of an 8-wk handgrip training period. MVC was also assessed every 2 wk, with forearm volume and girth assessed at the beginning and end of the 8-wk training period.

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We used two 10-MHz multifrequency linear array probes, attached to high-resolution ultrasound machines (T3000; Terason, Burlington, MA) to simultaneously assess diameter and velocity changes. A detailed description of this technique is provided elsewhere (14). Heart rate and mean arterial pressure were determined from an automated sphygmomanometer (Dinamap; GE Pro 300V2). Measurements were performed for at least 1 min.

**Brachial artery wall thickness and diameter.** A 10-MHz linear array transducer attached to a high-resolution ultrasound machine (T3000; Terason) was used to assess lumen diameter and wall thickness of the brachial artery in the distal third of the upper arm (16, 28). Measurements were performed by experienced vascular sonographers. Measurements of the diameter were performed simultaneously (and at the same site) as arterial wall thickness. Clearly demarcated intima-medial boundaries were provided by perpendicular incidence of the imaging ultrasound beam in relation to the orientation of the vessel. Images were optimized by using contrast controls on the ultrasound machine. Ultrasound parameters were set to optimize longitudinal B-mode images of the lumen/arterial wall interface. We recorded the brachial artery diameter and wall thickness for at least 10 s.

**Anthropometry.** Maximal forearm girths were assessed using a Lufkin diameter tape (Lufkin, Mexico), and forearm volume changes. Measurements were determined by immersion of the forearm in water. Images were captured using contrast controls on the ultrasound machine. Ultrasound parameters were set to optimize longitudinal B-mode images of the lumen/arterial wall interface. We recorded the brachial artery diameter and wall thickness for at least 10 s.

**Data Analysis.**

**Blood flow.** Postrace analysis of brachial artery blood flow was performed using custom-designed, edge-detection, and wall-tracking software that is independent of investigator bias (47). Recent papers contain detailed descriptions of our analytical approach (3, 14). From synchronized diameter and velocity data, blood flow [the product of lumen cross-sectional area and Doppler velocity (v)] was calculated at 30 Hz. Shear rate (an estimate of shear stress without viscosity) was calculated as four times mean blood velocity/vessel diameter.

**Diameter and wall thickness.** Brachial artery images were analyzed using custom-designed, edge-detection, and wall-tracking software. This DICOM-based software is largely independent of investigator bias and has been previously described in detail (34, 35). Briefly, the initial video signal was encoded and stored as a digital file, converted to a DICOM file after the completion of the test. Software analysis was performed at 30 Hz using an icon-based graphical programming language and toolkit (LabView 6.02, National Instruments, Austin, TX). By identifying a region of interest on each first frame of every individual study, capturing both walls of the artery, we made an automated calibration of diameters on the B-mode image. Within the

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**Experimental Procedures**

**Acute effects of handgrip exercise.** Subjects rested for 15 min in a comfortable chair in the upright position in a quiet, temperature-controlled room. Baseline bilateral brachial artery diameter and velocity were recorded using high-resolution duplex ultrasound for at least 1 min. Subsequently, subjects performed bilateral handgrip exercise using identical dynamometers at a cadence of 30 contractions/min for 30 min. While both arms were simultaneously exposed to identical handgrip exercise, a cuff was placed around one forearm and inflated to a sub-diastolic pressure of 60 mmHg. The placement of this cuff around the left or right forearm was randomized between subjects. Brachial artery blood flow and shear were recorded, above the cuff, during the handgrip exercise intervention in both the cuffed and noncuffed arms. Data generated from this analysis were recently published (44) in a study that examined the acute effects of shear stress on endothelial function. It is included here solely to establish that we successfully manipulated our independent variable, shear stress, between the cuffed and noncuffed limbs.

A subgroup underwent bilateral blood pressure measurement while undergoing an identical protocol as that described above (n = 7). Bilateral blood pressure was taken before and at 5-min intervals during the bilateral handgrip exercise using an automated blood pressure device around the upper arm (Dinamap; GE Pro 300V2, Tampa, FL). Blood pressure during exercise was calculated as the mean of three measurements using a handgrip dynamometer (Stoelting, Wood Dale, IL).

**Effects of handgrip training.** Exercise training was performed over an 8-wk period with subjects visiting the laboratory 3 times/wk and performing one session at home. Each laboratory session was supervised and consisted of 30 min of simultaneous handgrip exercise (30 contractions/min) at 30% MVC for 4 wk, 40% for 2 wk, and the final 2 wk at 50% MVC. Across the exercise training period, there was 90% adherence to the training sessions. During each 30-min training session, a pneumatic blood pressure cuff was placed below the cubital crease. Three measurements of girth and volume were taken on each arm, and the mean was derived. MVC of both forearms was assessed simultaneously (and at the same site) as arterial wall thickness. Clearly demarcated intima-medial boundaries were provided by perpendicular incidence of the imaging ultrasound beam in relation to the orientation of the vessel. Images were optimized by using contrast controls on the ultrasound machine. Ultrasound parameters were set to optimize longitudinal B-mode images of the lumen/arterial wall interface. We recorded the brachial artery diameter and wall thickness for at least 10 s.

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identified region of interest in the diameter image, a pixel-density algorithm automatically identified the angle-corrected near and far wall e-lines for every pixel column for diameter assessment. The same algorithm was used to identify the far wall media-adventitia interface. The detection of the near and far wall lumen edges and the far wall media-adventitia interface was performed on every frame selected. This technique has a good interobserver reproducibility, with a coefficient of variation of 5.1% (34). All files were checked on quality of analysis by at least one independent researcher who was blinded for when (0, 2, 4, 6, and 8 wk) and where (cuff vs. noncuffed) the file was recorded.

Statistics

Statistical analyzes were performed using SPSS 17.0 (SPSS, Chicago, IL). The acute effect of exercise on brachial artery blood flow and shear rate between the cuffed and noncuffed limb was compared using a paired t-test. Repeated-measures ANOVA and post hoc paired t-tests were used to examine whether the effect of the 8-wk exercise training (time; 0, 2, 4, 6, and 8 wk) on our primary outcome parameters differed between limbs (cuff; cuffed vs. noncuffed). Post hoc comparisons were made if a significant training or interaction effect was found. All data are reported as means ± SE, and statistical significance was assumed at P ≤ 0.05. A Bonferroni test was used to control for multiple comparisons, where the pertinent comparisons were between baseline data and that at weeks 2, 4, 6, and 8, respectively (i.e., 4 comparisons, leading to a P value of 0.0125 to be considered significant for post hoc comparisons).

RESULTS

Acute Effect of Handgrip Exercise

Baseline brachial artery mean shear rate and mean arterial pressure were similar between the limbs (t-tests, P = 0.97 and 0.13, respectively, Fig. 1). Handgrip exercise induced a significant increase in mean shear rate in the noncuffed arm (Fig. 1). Despite the performance of identical exercise with the contralateral limb, cuff inflation to 60 mmHg resulted in no change in mean shear rate compared with resting data (Fig. 1). Mean arterial blood pressure increased significantly in both arms (P < 0.001, Fig. 1). In contrast to the shear data, the increase of mean arterial pressure in the noncuffed arm was similar to that observed in the cuffed arm (11 ± 9 vs. 12 ± 8 mmHg, P = 0.82). Handgrip exercise induced a significant increase in heart rate from 67 ± 16 to 74 ± 14 beats/min (P = 0.027).

Chronic Effects of 8 wk of Handgrip Training

There were no significant differences at baseline between the arms in terms of girth, volume, or strength (Table 1). MVC increased significantly in both arms after 8 wk of handgrip training (P < 0.001), and both limbs also demonstrated a similar increase in forearm volume and girth (P < 0.05).
Localized handgrip training induced significant decreases in wall thickness across the exercise training period (Fig. 2). Post hoc tests revealed a significant effect of exercise training on the wall-to-lumen ratio after 6 and 8 wk (P < 0.0125). The change in wall-to-lumen ratio was not significantly different between the cuffed and the noncuffed forearm (Fig. 2).

**DISCUSSION**

In the present study we examined the role of shear stress in arterial wall remodeling in response to handgrip exercise training in healthy subjects. The typical increase in blood flow and shear stress associated with handgrip exercise was significantly attenuated by cuff inflation during exercise in the contralateral limb, enabling a comparison of the impact of shear stress on adaptations of the artery wall associated with exercise training. We found that 8 wk of localized exercise training resulted in a time-dependent decrease in wall thickness and that the manipulation of shear stress did not modify this effect. Our study therefore indicates that shear stress is not obligatory for conduit artery wall remodeling during exercise training in healthy subjects.

Cross-sectional comparisons and exercise training interventions have generally reported that exercise decreases conduit artery wall thickness in middle-aged and older healthy men (9, 29), including those with cardiovascular risk factors or disease (16, 28). In keeping with these results, our subjects demonstrated a decrease in artery wall thickness after exercise training, which became significant following 6–8 wk of training. This observation fits with the idea that prolonged exercise is necessary to induce changes in wall thickness, whereas changes in arterial function may follow a different time course (43, 45). Evidence in animals and humans suggests that exercise training in healthy men leads to an initial improvement in vascular function, followed by adaptations in vascular structure (22, 24, 36, 43, 45). Since wall thickness reflects structural vascular adaptation, the decrease in brachial artery wall thickness at the end of the training program reinforces the evolving theory of time-dependent changes in vascular function and structure to exercise training (43, 45).

Despite the decrease in shear rate during exercise training in the cuffed arm, brachial artery wall thickness changed similarly in both limbs across the 8-wk exercise program. This suggests that shear rate is not obligatory for arterial wall remodeling across an 8-wk training period in humans, a finding that is consistent with another recent study in which we compared the dominant and nondominant limbs of elite squash players (38) and observed differences in arterial diameter but...
not wall thickness. Since the dominant and nondominant arms of these elite racquet sportsmen are chronically exposed to different levels in shear stress, we concluded that shear stress does not induce wall thickness differences between limbs following chronic exposure to intense exercise.

Our study raises the question of which mechanism(s) may contribute to exercise-induced adaptation in wall thickness in healthy volunteers. Local differences in ischemia and/or metabolites may be present. However, we measured arterial wall thickness above the ischemic zone, which makes it unlikely that local metabolic factors explain our results. However, blood flow may also be controlled by remote cell-to-cell communication via gap junctions among vascular beds (10, 39). We cannot exclude the possibility of some retrograde arterial communication despite the large distances between the forearm microvasculature and brachial artery in our experimental model. Another possibility is that repeated exposure to limb ischemia may lead to remote preconditioning (4, 27). However, it seems unlikely that significant local ischemia which could lead to remote effects on brachial artery wall thickness would have resulted from our 60-mmHg cuff inflation during exercise training. Another mechanism that potentially contributes to arterial wall remodeling relates to exercise-induced inflammation. A previous study found a systemic inflammatory response and systemic release of mediators of angiogenesis following unilateral forearm exercise (31). Such systemic changes, induced by local forearm exercise, may contribute to adaptations in the arterial wall seen in both limbs in our study. Furthermore, systemic circulating factors, such as endothelial progenitor cells or antioxidative enzymes, may contribute to our findings. However, it seems unlikely that local handgrip exercise would result in the release of systemic factors which have a significant impact on artery wall thickness.

Our simultaneous bilateral measurements and training stimuli suggest that our findings may result from systemic hemodynamic changes. For example, blood pressure, and the consequent cyclic change in transmural pressure across the arterial wall, may contribute to arterial wall remodeling (23). Indeed, bilateral handgrip exercise evoked a significant increase in blood pressure, which was comparable between the cuffed and noncuffed arms. There is some suggestion that a repetitive, cyclic increase in circumferential strain in the artery wall, as a result of exercise-induced pressure changes, may be associated with antiatherogenic effects [e.g., endothelial nitric oxide synthase expression/activity (1, 2) and endothelium-derived hyperpolarizing factor synthase expression (37)]. Conversely, chronically elevated pressure is associated with increased wall thickness and may contribute to elevated peripheral resistance and hypertension (11, 12). Laughlin et al. (23) recently attempted to rationalize this data by hypothesizing that the brief, cyclic exposure to pressure/circumferential strain, such as that associated with intermittent exercise bouts, changes the balance toward antiatherogenic vascular adaptation. Our data, involving similar decrease in brachial artery wall thickness in response to bilateral episodic increase in arterial pressure, provide some support for this proposal.

**Limitations**

A potential limitation of our study relates to our measurement of wall thickness at rest such that it may be affected by factors which influence basal tone. Removing basal tone, for example via the administration of a potent vasodilator such as glyceryl trinitrate, may reveal differences in arterial diameter or wall thickness that are not apparent in resting measures (17). Whether basal tone plays a role in the regulation of arterial wall thickness, especially after short bouts of physical activity, is currently unknown. In a subset of our subjects \( n = 7 \), we examined brachial artery wall thickness during glyceryl trinitrate before and after exercise training. We found a \( 13.5 \pm 6.2\% \) decrease in wall thickness before training, which was not different after training \( (12.8 \pm 5.2\%, P = 0.79) \). This suggests that differences in baseline brachial arterial wall thickness before and after training are not importantly influenced by removal of basal tone. Our simultaneously recording of images from both arms also negates the potential role of any central effects on arterial tone preferentially affecting one limb.

Most previous studies have examined carotid or femoral artery wall remodeling, given its predictive value for cardiovascular risk (5) and vulnerability for plaque formation. For obvious reasons, the design adopted in this study could not be applied to the carotid artery, while practical issues impeded the use in the femoral artery. Nonetheless, previous studies have demonstrated the clinical significance of brachial artery wall thickness in terms of the prediction of future cardiovascular events (25, 26), and brachial artery function is also a strong prognostic index (15, 18). Moreover, a recent study found that exercise training in healthy older subjects has a similar effect on upper and lower limb conduit artery wall thickness (16), suggesting that our observation may be of clinical importance and relates to other conduit arteries.

In conclusion, our results demonstrate that exercise training in healthy young men leads to a time-dependent change in brachial artery wall thickness. Moreover, we provide evidence that exercise-induced increases in shear, an essential hemodynamic stimulus for exercise-induced adaptations in vascular function, is not obligatory for conduit artery wall remodeling during exercise training in healthy subjects. Adaptations in wall thickness in response to exercise training in healthy subjects apparently relate to systemic, rather than localized, hemodynamic stimuli.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**REFERENCES**

H246 SHEAR STRESS, WALL THICKNESS, AND EXERCISE TRAINING


