Endothelial function of young healthy males following whole body resistance training


1Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada; and
2Department of Physiology, University Medical Center Nijmegen, Nijmegen, The Netherlands

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The endometrium of conduit arteries has been identified as a primary target of injury from mechanical forces and processes that increase cardiovascular risk such as hypertension (29). Because the health of the endometrium plays a pivotal role in the maintenance of vascular tone and reactivity (28), the importance of maintaining an intact and functional vascular endometrium is obvious. Endothelial dysfunction has been observed in those with coronary artery disease (12) and chronic heart failure (11, 18, 21) and in apparent healthy elderly individuals with no overt signs of cardiovascular disease (32). Importantly, brachial artery endothelial dysfunction has been well correlated with disease progression of the coronary arteries in patients with coronary artery disease (18).

Almost without exception, impaired endothelial function (endothelial-dependent dilation of <4%) is improved with an aerobic exercise intervention. These findings have been observed in young healthy men both cross sectionally (30) and after intervention studies (7, 14, 15, 20, 30). Furthermore, increased endothelial function has been observed systemically even when exercise was limited to the lower limb (14).

Favorable cardiovascular effects of aerobic exercise training are well established; however, little is known regarding the effect of resistance training on endothelial function independent of aerobic exercise. In fact, studies of resistance training and blood pressure improvements have been equivocal (19), and recent cross-sectional and longitudinal studies in resistance-trained athletes have shown reduced central artery compliance (25, 27). Given the increasing emphasis on performance of resistance exercise for health (1), it is relevant to have data regarding the effect of this form of exercise on endothelial function. Studies evaluating the combined effect of aerobic and resistance training have been conducted in patients suffering from chronic heart failure (24) and Type 2 diabetes (23) with favorable results. Maiorana and colleagues have shown not only improvements in conduit artery function but also improvements in resistance vessel function in both congestive heart failure (24) and Type 2 diabetic patients (23). Despite these beneficial effects, the contribution of the resistive component, independent of aerobic effects, to improved vascular endothelial function is not known.

Therefore, the aim of the present study was to evaluate the effects of whole body resistance exercise training on endothelial function in a population of young healthy men. To our knowledge, this has not been addressed previously. We hypothesized that the adaptation in vascular function would be dependent on the type of training stimulus. For example, the persistently elevated blood flow, under low pressure, associated with aerobic exercise would create a shear stress that would appear to be the main reason for improved vascular endothelial function (7, 12, 14, 18). In comparison, resistance exercise is associated with only transient postcontraction high flows, under high pressure, which would result in an entirely different shear stress stimulus. Our hypothesis was that shear stress profile associated with resistance exercise would be transient yet large enough to induce significant improvements in endothelial function. We chose to assess conduit artery endothelial function using a nonpharmacological flow-mediated dilation (FMD) technique, which simulates normal physi-
iological demands, such as an increase in blood flow, and is a clinically relevant measure of vascular reactivity. Resistance vessel function and capacity was assessed using simultaneous measurements of blood flow.

MATERIALS AND METHODS

Subjects. Twenty-eight young healthy men (height: 1.79 ± 0.02 m; weight: 84.1 ± 2.4 kg), average age of 23 ± 3.9 yr (means ± SE), participated in this study. All participants were physically active yet had not participated in a structured resistance training protocol for at least 6 mo before the beginning of testing. All subjects were normotensive (<140/90 mmHg), were nonobese, had normal fasting blood cholesterol and triglycerides concentrations, and were free of overt chronic diseases as assessed by medical history, physical examination, and standard blood lipid screening. The McMaster University Research Ethics Board approved the experimental protocol, and all participants provided written, informed consent before participating in the study.

Resistance training protocol. All participants completed up to 60 sessions of resistance training at a frequency of five times per week (Monday to Friday) using a 3-day rotating design. Each day of the rotation consisted of exercises that targeted a specific group of muscles. The 3 days were divided into upper body “pull,” “push,” and “leg” days. Pushing exercises consisted of shoulder press, horizontal bench press, vertical bench press, triceps push down, and chest flys. Pulling exercises consisted of seated lat pull down, wide-grip seated row, narrow grip seated row, biceps cur, and seated rear flys. Finally, leg exercises consisted of an incline double leg press, leg curl, seated leg extension, and standing calf raises. Abdominal and lower back extension exercises were also included in the protocol every 3 days. Training was conducted in the student fitness center on the McMaster University Campus. All pieces of equipment were motion-guided Badger Magnum 2001 series (Magnum Fitness Equipment, South Milwaukee, WI) machines using weight plates for resistance. To minimize the contaminating effect of endurance exercise training on measurements of endothelial function, participants who were aerobically active more than two times per week were excluded. Those participants who did engage in a small amount of aerobic activity were instructed to simply maintain their level of training and those who were not aerobically trained were asked to refrain from such activities until after the completion of the exercise-training program.

One-repetition maximum lifts. To maintain an adequate resistance training stimulus and to track strength gains throughout the training program, one-repetition maximum lifts were performed before, at 4 wk, at 8 wk, and after completion of the program. One-repetition maximum testing was performed at each time point, coordinated to correspond with each subgroup of exercises within the split routine.

Progression of exercise program. The progression of the resistance exercise stimulus was from 2 sets of 10–12 repetitions during the first 2 wk to 3 sets completed for the remainder of training. By week 6, the third set was performed to volitional failure and weights were adjusted to ensure failure by six to eight repetitions. Finally, by week 12, participants performed four to six repetitions with loads exceeding 90% of one-repetition maximum. This protocol was employed with the goal of inducing maximal muscle hypertrophy. Throughout the program, 2-min rest periods were incorporated between sets. Training sessions lasted ~60 min depending on the number of sets required.

Testing protocol and measurements. Measurements of brachial endothelial function, postocclusion reactive hyperemic blood flow, postocclusion shear rate, and mean arterial diameter were conducted twice before (Pre), once during week 7 (Mid), and once after the completion of resistance training (Post) during week 13. All measurements were conducted according to identical control conditions. Participants were tested at the same time of day (within ~2 h of the same time) and were always 4 h postprandial after the consumption of an identical commercially available standardized meal replacement drink (237 ml BOOST, Mead Johnson Nutritional, Ottawa, ON, Canada). All participants were asked to abstain from caffeine and nicotine for at least 12 h before testing (2 subjects smoked ~12 cigarettes/day) and ~24 h from strenuous exercise. Measurements were taken while subjects were in the supine position in a temperature-controlled (22–24°C) room.

Endothelial function protocol. Brachial vascular endothelial-dependent function was evaluated using FMD according to currently established guidelines (8). Briefly, a pneumatic cuff connected to a rapid inflation system (model E20 and AG101, Hokanson, Bellevue, WA) was placed around the forearm 2–4 cm distal to the antecubital fossa. The cuff was inflated to a pressure of at least 200 mmHg to ensure complete occlusion of the brachial artery. Occlusion was maintained for a period of 4.5 min. Longitudinal brachial artery images and blood velocity measurements were made using a 10-MHz linear array pulse Doppler ultrasound probe (System SiVe, GE Medical Systems, Horten, Norway), which was positioned ~3–5 cm proximal to the antecubital fossa. Continuous video recording of the image of the brachial artery was obtained from 15 s before cuff deflation until 70 s after cuff deflation. In addition, a 16.7-s digital video clip was stored at 70 s after deflation. This digital video clip obtained digital images at a rate of 10 Hz from 53 to 70 s after cuff deflation. In parallel to the imaging of the brachial artery, mean blood velocity (MBV) was obtained using the duplex function of the previously described linear array probe from 15 s before cuff deflation until 15 s after cuff release to determine peak and mean postocclusion blood flow and shear rates. The raw audio signal corresponding to blood velocity was output from the Doppler ultrasound system into a transcranial Doppler system (model Neurovision 500M TCD, Multigon Industries, Yonkers, NY) running spectral analysis software. A fast Fourier transform was applied to the raw audio signal to determine MBV continuously. Blood velocity was corrected for insonation angle during postacquisition analysis. After analog-to-digital conversion of ECG and MBV (Powerlab model ML795, ADInstruments, Colorado Springs, CO), these physiological signals were collected on a personal computer (IBM Netvista ×86-compatible processor, White Plains, NY) using commercially available software (Chart 4.2, AD-Instruments).

Resting mean brachial arterial diameter. Two single heart cycle digital video clips of the brachial artery were loaded and visualized on a personal computer (Pentium 4, 2.66 GHz, clone) using specific image analysis software (AMS II, Chalmers University of Technology, Göteborg, Sweden). A clear portion of the image was chosen for automated analysis by the investigator. The region of interest of the brachial artery was kept consistent at all time points within each subject by locating similar anatomic landmarks (i.e., collateral circulation). The investigator sized and positioned the region of interest to encompass both near and far blood vessel walls and initiated a command to permit the program to determine mean diameter from leading edge to leading edge throughout subsequent frames of the digital video clip. The software program performed a minimum of 100 measurements of the artery diameter within the region of interest to obtain a mean arterial diameter for each frame of the digital video clip. The user, if needed, could make corrections of the various borders manually. To obtain a measurement of mean artery diameter for one heart cycle, an average was calculated from all but the last frame (since it was at the same time point as the first) of one video clip. Mean heart cycle diameters from the two video clips were subsequently averaged to obtain mean brachial artery diameter.

Brachial FMD. Digital video acquired from 53 to 70 s after cuff deflation was used to determine maximal dilation of the brachial artery. Using automated-user input analysis software (AMS II), diameters at end-diastole were acquired from leading edge to leading at all time points. This technique allowed between 15 and 20 consecutive measurements of end-diastolic diameter, thus reducing the variability of the technique. An average of these measurements was taken and compared with the average of two resting measurements of end-
diastolic diameter, which were made ~1 min before cuff inflation. These values gave a relative percent dilation.

Postocclusion reactive hyperemia. As previously described, blood velocity measurements were acquired from 15 s before until 15 s after cuff release. Measurements of peak beat and 10-s average flow were calculated (vessel cross-sectional area \( \times \) MBV) and used to quantify the hyperemic response. Also, peak beat and 10-s average shear rate were determined as (4 \( \times \) MBV)/mean diameter.

Normalized FMD. Resultant measurements of FMD were normalized to mean shear rate since the amount of dilation has been shown to depend on the resultant hyperemic flow stimulus as represented by shear rate.

Statistical analysis. All variables were analyzed using a repeated-measure ANOVA across the three time points of measurement (Pre, Mid, Post). When a significant main effect was noted, a Tukey’s honestly significant difference post hoc test was used for subsequent analysis. Significance for all analysis was set at \( P \leq 0.05 \). All values are presented as means ± SE.

RESULTS

Participants exhibited a significant progression from Pre to Mid and from Mid to Post increases in strength not attributable to a learning effect since familiarization sessions were conducted before the start of training. Mean strength gains Pre to Post for pulling exercises was 40 ± 0.02%, for pushing exercises was 50 ± 0.02%, and for leg exercises was 61 ± 0.02% (all \( P < 0.01 \)). Also, significant increases in body mass index and body weight were noted from Pre to Post.

Resting mean brachial artery diameter. Mean brachial artery diameter significantly increased from Pre to Mid with resistance exercise training and remained significantly elevated at Post (Fig. 1).

Peak and 10-s average reactive hyperemia. Peak forearm blood flow significantly increased (\( P < 0.01 \)) above Pre levels by Mid and remained elevated at Post (Table 1).

Table 1. Brachial postocclusion blood flow and shear rates at Pre, Mid, and Post

<table>
<thead>
<tr>
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<th>Pre</th>
<th>Mid</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak brachial blood flow, ml/min</td>
<td>247.5±14.0</td>
<td>331.1±18.5*</td>
<td>290.5±21.0*</td>
</tr>
<tr>
<td>10-s average blood flow, ml/min</td>
<td>226.4±12.9</td>
<td>302.4±17.5*</td>
<td>269.1±18.9*</td>
</tr>
<tr>
<td>Peak shear rate, s(^{-1})</td>
<td>38.6±1.5</td>
<td>43.1±1.9</td>
<td>39.2±2.1</td>
</tr>
<tr>
<td>10-s average shear rate, s(^{-1})</td>
<td>35.2±1.4</td>
<td>39.0±1.5</td>
<td>36.3±1.8</td>
</tr>
</tbody>
</table>

Data are means ± SE. Pre, pretraining; Mid, 6 wk of training; Post, 13 wk of training. *Significant difference from Pre (\( P < 0.05 \)).

DISCUSSION

The present study is the first to prospectively examine, using a longitudinal design, the effects of resistance exercise training on measurements of vascular endothelial function, postocclusion blood flow, and arterial remodeling. The most relevant findings include an increase in mean brachial artery diameter, no change in relative and normalized brachial FMD (a measure of vascular endothelial function), and an increase in postocclusion blood flow with exercise training. These results show that short-term (12 wk) resistance training in healthy young men can induce an increase in resting arterial diameter, which appears to represent a stable adaptation. In addition, the greater postocclusion blood flow suggests resistance vessel (arteriolar and/or capillary) proliferation or enhanced resistance vessel endothelial function, which may be a significant clinically relevant finding.

Arterial remodeling. The increase of resting mean brachial artery diameter at both Mid and Post suggests unique adaptations that may be mediated by persistent chemical stimuli that affect arterial tone (NO, endothelin-1) and/or physical structural changes to the vessel itself. Alterations in sympathetic tone or other regulators of vasoconstriction and dilation may considerably alter resting arterial diameter. However, few data support a role for altered sympathetic tone after resistance
training (6), and no studies to our knowledge have evaluated the exclusive effects of resistance training on circulating NO or endothelin-1, whereas little change has been observed in other vasoactive substances such as vasopressin or the renin-angiotensin system (5).

Because the role of functional adaptations (NO-mediated vessel relaxation, sympathetic tone) in the regulation of arterial vessel size would appear to be limited, alterations of mean brachial artery diameter are likely structural and mediated by the transient shear stresses after exercise. Similar to the mechanism proposed after aerobic exercise training studies (9, 26), shear stress caused by reactive hyperemia during the exercise session likely mediates NO release and subsequent structural adaptations to ensure peak shear rate maintenance (10, 22, 31). Furthermore, alterations may be specific to the reductions of intima-media thickness. Unfortunately, the data do not allow a distinction between vessel remodeling and intima-media thickness alterations because intima-media thickness measurements were unable to be made with adequate precision in the brachial artery. Therefore, further studies evaluating the longitudinal effects of resistance training on vasoactive substances, and the responsiveness to these substances, are needed to better understand vessel remodeling under these circumstances.

Vascular endothelial function. As previously mentioned, conduit artery vascular endothelial function was unaltered when described as a relative measurement from baseline (change from rest). In addition, because postocclusion shear rate was not different at any testing time point, it would be reasonable to assume that the FMD normalized to mean shear rate would also be unaltered. Predictably, this was what we observed, which illustrates that there was no change in brachial vascular endothelial function with resistance exercise training. At the level of the resistance vessels, endothelial-dependent function may have been improved as reflected by an increase in postocclusion blood flow after training. This observation would support similar observations in previous studies involving combined aerobic and resistance training (24, 23). Because blood flow is regulated at the level of the resistance vessels, this finding may have important clinical relevance. In particular, blood flow delivery in response to a physiological stimulus-like exercise is limited in numerous pathological conditions, including congestive heart failure (4) and peripheral artery disease (3). Thus resistance training may be useful as a therapeutic modality to enhance resistance vessel function and warrants further attention.

Because there was no observable effect of resistance exercise training on brachial endothelial function, one might suggest that improvements in conduit artery endothelial function are limited. Perhaps shear rates in the brachial artery were simply too small and transient to warrant adaptations of conduit artery endothelial function. It should be noted that alterations in resistance vessel function may not be observed in conduit arteries supplying the vascular beds that exhibit enhanced resistance vessel function (13). In contrast, coronary

![Fig. 3. Changes of brachial postocclusion peak blood flow (A), 10-s average blood flow (B), peak shear rate (C), and 10-s average shear rate (D) at Pre, Mid, and Post. Values are means ± SE. *Significant difference from Pre (P < 0.05).]
artery dilation capacity may have been improved as a result of training since this vascular bed is likely experiencing a continuous and more frequent increase in shear stress compared with the limbs, which are used only intermittently throughout a training session. Indeed, coronary vasodilatory capacity may not be reflected at all times via measurements made in the periphery as shown by Anderson and colleagues (2), who demonstrated a weak correlation with an r value of 0.36. Thus an increase in coronary artery dilatory capacity may have occurred but was not reflected in measurements at the brachial artery. Evidently, training studies in which invasive evaluations of coronary vascular endothelial function were made would be useful.

One other possible explanation regarding the lack of improvement in brachial artery vascular endothelial function is that this cohort exhibited fully functional endothelium before training. Therefore, improvements may not have been possible. Our participants may not have experienced an adequate shear stress stimulus with resistance exercise to enhance endothelial NO synthase expression and subsequently increase NO availability after occlusion during the FMD protocol. We cannot comment on the responsiveness to NO, which would have been revealed had we performed pharmacological (i.e., nitroglycerin administration) stimulation of endothelial function. However, we chose to assess vascular endothelial function using FMD, since the postocclusion response represents an integrated response of all systems (i.e., response to a high shear stress, NO availability, and responsiveness to NO). We believe that further longitudinal studies are needed to fully assess the beneficial effects of resistance training on vascular function. Such studies would combine nonpharmacological (FMD) and pharmacological tests of vascular endothelial function as well as direct measures of coronary artery responsiveness.

Postocclusion blood flow and shear rate. The significant increase of postocclusion blood flow at Mid and Post compared with Pre is likely related to enhanced resistance vessel endothelial function. However, another mechanism may also contribute to the observed increase in postocclusion blood flow. Because measurements of flow made in the conduit feed artery (brachial) do not allow inference into the downstream destinations of blood flow, two possible explanations exist. First, as previously described, the total downstream cross-sectional area may be increased through greater resistance vessel dilation in response to occlusion. Alternatively, the total capillary/arteriolar cross-sectional area may be increased through capillary/arteriolar proliferation. Capillary density has been observed in previous studies involving resistance exercise training (16) and may coincide with muscle hypertrophy of the forearm. One should also note that a greater muscle mass distal to the occlusion site would likely increase metabolite accumulation during ischemia and consequently provide a greater stimulus for blood flow upon cuff release. Thus either enhanced endothelial function at the level of the resistance vessels or a greater number of these vessels may contribute to the increased postocclusion blood flow. Both mechanisms reveal beneficial adaptations to the vascular bed and ultimately result in greater perfusion after an ischemic stimulus.

General discussion. We acknowledge that measurements on a nonexercising control group were not made with similar temporal frequency. We believe, for a number of reasons, that our results are still valid and relevant. First, to improve the stability of the Pre measures, we had two familiarization sessions to reduce the variability associated with apprehension that our subjects may have had, which could have affected sympathetic activity and thus endothelial-dependent dilation (17). Second, the same investigator, while blinded to condition, made all measurements of vascular variables at Pre, Mid, and Post. Third, we included a large number of subjects, which resulted in normally distributed data and high statistical power, which improved our ability to detect differences if they were present.

In conclusion, these findings show that 12 wk of whole body resistance exercise training does not affect brachial vascular endothelial function in young healthy men as measured using FMD; however, brachial artery vessel diameter increases and postocclusion blood flow increases with this training modality. Clinically, these results support resistance exercise training as a stimulus that may enhance resistance vessel function. Further studies that combine measurements of capillary density and resistance vessel function need to be conducted before this conclusion can be solidified. Also, studies involving invasive measurements of vascular endothelial function may provide further details regarding the mechanisms responsible for enhanced blood flow after resistance training.

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GRANTS

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REFERENCES


