HIGHLIGHTED TOPIC | Skeletal and Cardiac Muscle Blood Flow

Comparison of resistance and conduit vessel nitric oxide-mediated vascular function in vivo: effects of exercise training

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Green, Daniel J., Jennifer H. Walsh, Andrew Maiorana, Valerie Burke, Roger R. Taylor, and J. Gerard O’Driscoll. Comparison of resistance and conduit vessel nitric oxide-mediated vascular function in vivo: effects of exercise training. J Appl Physiol 97: 749–755, 2004. First published April 16, 2004; 10.1152/japplphysiol.00109.2004.—Exercise training improves vascular function in subjects with cardiovascular disease and risk factors, but there is mounting evidence that these vascular adaptations may be vessel bed specific. We have therefore examined the hypothesis that exercise-induced improvements in conduit vessel function are related to changes in resistance vessel function. Endothelium-dependent and -independent conduit vessel function were assessed using wall-tracking of high-resolution brachial artery ultrasound images of the response to flow-mediated dilation (FMD) and nitroglycerine [glyceryl trinitrate (GTN)] administration. Resistance vessel endothelium-dependent and -independent function were assessed using intrabrachial administration of acetylcholine (ACh) and nitroprusside (SNP). Randomized crossover studies of 8-wk exercise training were undertaken in untreated hypercholesterolemic (n = 10), treated hypercholesterolemic (n = 10), coronary artery disease (n = 8), and Type 2 diabetic subjects (n = 15). Exercise training significantly enhanced responses to ACh (P < 0.05) and FMD (P < 0.0001). There were no significant changes in either SNP or GTN responses. The correlation between ACh and FMD responses at entry was not significant (r = 0.186; P = 0.231), and training-induced changes in the ACh did not correlate with those in FMD (r = −0.022; P = 0.890). Similarly, no correlation was evident between the SNP and GTN responses at entry (r = −0.010; P = 0.951) or between changes in these variables with training (r = −0.211; P = 0.191). We conclude that, although short-term exercise training improves endothelium-dependent nitric oxide-mediated vascular function in both conduit and resistance vessels, the magnitude of these improvements are unrelated.

acetylcholine; flow-mediated dilation; resistance vessel; conduit artery

THE ENDOTHELIUM, STRATEGICALLY located at the interface between the circulating blood and vascular wall, homeostatically regulates vascular tone and inflammatory, thrombogenic, and mitogenic processes, and endothelial dysfunction is the earliest detectable manifestation of atherosclerotic disease. Endothelial dysfunction is present in subjects with cardiovascular risk factors (4, 5, 7, 9) and disease (27, 38) and predicts cardiovascular events (1, 14, 36, 41). Furthermore, interventions that improve cardiovascular mortality and morbidity are also associated with improved endothelial function (17, 21, 32, 33) and improvement in endothelial function predicts prognosis (28). Recent state-of-the-art reviews in peak cardiovascular journals have concluded that in vivo assessment of endothelial dysfunction, a marker of the integrated effect of cardiovascular risk factors on the vasculature (44), provides additional prognostic information to that derived from conventional risk factors assessed (3, 40) and may represent a potential barometer of cardiovascular risk (41).

The two most common methods of assessing endothelial dysfunction in vivo involve the construction of blood flow response curves to local intra-arterial infusion of agents that stimulate endothelium-dependent and -independent vasodilation and the measurement of shear stress and glyceryl trinitrate (GTN)-mediated large artery vasodilation by using high-resolution ultrasound (11). The former method typically involves strain gauge plethysmographic measurement of forearm blood flow responses to intrabrachial drug administration, most often to acetylcholine (ACh) and sodium nitroprusside (SNP). The latter noninvasive method directly images brachial artery responses to flow-mediated dilation (FMD) induced by a brief period of forearm ischemia and to sublingual GTN administration. In measuring total flow to the forearm, strain gauge plethysmography provides an assessment of resistance vessel function (37), whereas the ultrasound technique directly images larger conduit arteries. Few studies have directly compared conduit and resistance vessel function within individuals (10, 16, 24), and none has assessed whether changes in resistance vessel function relate to changes in conduit vessel function in response to an intervention. We have therefore pooled data from our laboratory’s exercise training studies involving subjects with cardiovascular disease or risk factors (26, 42, 43) to examine the hypothesis that exercise training-induced improvements in conduit vessel function are related to changes in resistance vessel function.

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METHODS

Subjects. A list of subject groups and their baseline characteristics are reported in Table 1. Inclusion criteria required untreated hypercholesterolemic subjects (UTHC; n = 10) to have initial total cholesterol >6.5 mmol/l and/or low-density lipoprotein (LDL) cholesterol >4.0 mmol/l, and none was taking any medication. Treated hypercholesterolemic subjects (TCH; n = 10) were taking 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitor in stable dose for at least 3 mo (8 on atorvastatin, 1 simvastatin, and 1 cerivastatin) and had documentation that total cholesterol was >6.5 mmol/l and/or LDL cholesterol >4.0 mmol/l before treatment. Four THC subjects were also taking aspirin, one was taking amiodipine (subject was normotensive for study duration), and one was taking constant-dose estradiol. Coronary artery disease (CAD) subjects (n = 8) had CAD requiring surgical (coronary artery bypass grafting) or nonsurgical revascularization (percutaneous transluminal coronary angioplasty). All were taking aspirin and were on HMG-CoA reductase inhibitor (statin) therapy, seven took β-blocking therapy, five took an angiotensin-converting enzyme (ACE) inhibitor, two took a proton pump inhibitor, and one each took a diuretic, a calcium channel-blocking drug, and cholestyramine. All but one of the Type 2 diabetic subjects (T2D; n = 15) were taking oral hypoglycemic medication, five were taking an ACE inhibitor, two were on statin therapy, and two were taking aspirin. None had evidence of micro- or macrovascular disease. For all subjects taking medication, treatment did not alter throughout the study period. All subjects were recruited from hospital clinics or via public advertisement.

Subjects were excluded if they were current smokers; had hyper tension (resting blood pressure >160/90 mmHg), hypercholesterolemia (total cholesterol >6.0 mmol/l or LDL cholesterol >4.0 mmol/l; except the UTHC subgroup), diabetes (except the T2D group) or asthma; displayed evidence of coronary or valvular heart disease from history, examination, and exercise electrocardiography (except the CAD subgroup); performed more than two sessions of light to moderate exercise per week; or were unable to exercise due to physical limitations. No subject had undergone a surgical procedure within the 3 mo preceding the study. The Royal Perth Hospital Ethics Committee approved the study protocols, and all subjects gave written, informed consent.

Study design. Study designs and assessment techniques for each group are described in individual papers and were almost identical (12, 26, 42, 43). After preliminary screening and baseline assessments, subjects were randomly assigned to remain sedentary or perform exercise training for 8-wk periods, followed by crossover.

Table 1. Baseline characteristics of untreated and treated hypercholesterolemic, CAD, and Type 2 diabetic subjects

<table>
<thead>
<tr>
<th></th>
<th>Untreated HC (n = 10)</th>
<th>Treated HC (n = 10)</th>
<th>CAD (n = 8)</th>
<th>Type 2 Diabetes (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>48.5 ± 10.2</td>
<td>55.4 ± 8.2</td>
<td>54.2 ± 4.8</td>
<td>52.1 ± 8.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.2 ± 3.4</td>
<td>27.0 ± 3.4</td>
<td>28.5 ± 4.1</td>
<td>29.6 ± 3.5</td>
</tr>
<tr>
<td>Waist-to-hip ratio, %</td>
<td>92.5 ± 5.5</td>
<td>88.3 ± 7.1</td>
<td>94.6 ± 9.2</td>
<td>99.3 ± 5.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>6.5 ± 0.4</td>
<td>4.5 ± 0.6</td>
<td>4.0 ± 0.9</td>
<td>4.7 ± 0.9</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>4.4 ± 0.5</td>
<td>2.6 ± 0.6</td>
<td>2.4 ± 0.6</td>
<td>2.4 ± 0.9</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.3 ± 0.4</td>
<td>1.2 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>Blood glucose, mmol/l</td>
<td>5.1 ± 0.3</td>
<td>5.1 ± 0.4</td>
<td>5.0 ± 0.8</td>
<td>5.0 ± 0.8</td>
</tr>
<tr>
<td>Glycated hemoglobin, %</td>
<td>5.2 ± 0.2</td>
<td>5.1 ± 0.4</td>
<td>5.2 ± 0.4</td>
<td>8.4 ± 1.4</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>117 ± 16</td>
<td>116 ± 14</td>
<td>126 ± 21</td>
<td>132 ± 17</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>70 ± 11</td>
<td>64 ± 9</td>
<td>71 ± 13</td>
<td>89 ± 12</td>
</tr>
<tr>
<td>Resting HR, beats/min</td>
<td>55 ± 8</td>
<td>62 ± 10</td>
<td>56 ± 8</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>VO₂peak, ml·kg⁻¹·min⁻¹</td>
<td>31.9 ± 6.4</td>
<td>26.0 ± 5.1</td>
<td>27.4 ± 6.0</td>
<td>23.0 ± 4.7</td>
</tr>
</tbody>
</table>

Values are means ± SD; n, no. of subjects. HC, hypercholesterolemia; CAD, coronary artery disease; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; VO₂peak, peak oxygen consumption.

The exercise training protocol and assessment procedures are outlined below. Subjects were requested to make no changes to their diet, therapy, or other routines for the duration of the study. Interventions commenced within 7 days of the completion of baseline assessments, and all repeat assessments, including resistance and conduit vessel function, were performed within 7 days of the cessation of exercise training or control periods.

Assessment of vascular function. Vascular function assessments were conducted in a quiet, temperature-controlled environment, at separate attendances for conduit and resistance vessel function. Repeat investigations were performed at the same time of day for individual subjects. Subjects fasted for 8 h, abstained from alcohol and caffeine for 12 h, and did not perform any exercise for 24 h before assessments.

Assessment of conduit vessel function. With the subject resting supine, the nondominant arm was extended and immobilized with foam supports and positioned at an angle of ~80° from the torso. Heart rate was continuously monitored with a three-lead electrocardiograph, and mean arterial pressure was determined from an automated sphygmomanometer (Dinamap 8100, Critikon, Tampa, FL) on the contralateral arm. Resting heart rate and blood pressure measures were recorded after 30 min of supine rest in all subjects.

A rapid inflation and deflation pneumatic cuff was thus positioned on the ipsilateral arm immediately distal to the olecranon process to produce a stimulus to forearm ischemia (6). A 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Aspen, Acuson, Mountain View, CA) was used to image the brachial artery in the distal one-third of the upper arm. When an optimal image was attained, the probe was held stable in a stereotactic clamp. Ultrasonic parameters were set to optimize longitudinal, B-mode images of the lumen-arterial wall interface.

After 20 min of rest, baseline images were recorded on a S-VHS video cassette recorder (SV-O-9500 MDP, Sony, Tokyo, Japan) over 2 min. The cuff pressure was then inflated to 200 mmHg for 5 min. Images were recorded 30 s before cuff deflation and for 2 min after deflation. After 10 min of rest, to allow arterial diameter to return to baseline, another 2-min baseline recording was made before a sublingual 400-μg spray dose of GTN with images recorded for a further 5 min.

Brachial artery diameters were analyzed by using custom-designed edge-detection and wall-tracking software, which minimizes investigator bias and has the power to detect an absolute change in FMD of 2% in a crossover design study with only six subjects (45). Briefly, an edge-detection algorithm averages >300 diameter measurements per frame, with 20–30 frames assessed per second. Those average diameter measures that coincide with the ECG R wave (also autodetected), that is, occurring at end diastole, were subsequently analyzed by using a third-order polynomial curve (45). FMD and GTN responses were then calculated from the peak value derived from this polynomial curve and related to the average of all R-wave-gated diameters collected during the baseline period preceding either the FMD or GTN manipulations. The mean intraobserver coefficient of variation of repeated measures of FMD using this software is 6.7%, which is significantly lower than that for traditional manual methods (45).
elevation were the same for repeat tests. An online microcomputer (SPG 16, Medasonics) sampled amplified output from the strain-gauges at 75 Hz, which was displayed in real time. A software program controlled cuff inflation and deflation as well as data acquisition, storage, and display to ensure blood flow measurements were synchronized with upper arm cuff inflation.

Arterial pressure was monitored continuously with a Hewlett-Packard monitoring system (model 78353A). ACh (Miochol, Ciba Vision, New South Wales, Australia) was infused at 10, 20, and 40 μg/min, each for 3 min, and SNP (David Bull Laboratories, Victoria, Australia) was infused at 2, 4, and 8 μg/min, each for 3 min by using a constant-rate infusion pump (model 770, IVAC). All solutions were prepared aseptically immediately before infusion.

The study protocol was identical for each subject. Baseline measurements were made 20 min after cannulation. Blood flow measurements were made after inflation of the wrist cuffs to 200 mmHg, to exclude the hands from the circulation, and by rapidly inflating the upper arm cuffs to 45 mmHg, to occlude venous flow, for 10 s out of every 15 s during baseline and drug infusion periods. For each data collection period, the last five measurements of FBF were averaged to give a representative flow for that period. There was a minimum of 10 min of rest between ACh and SNP infusions.

Exercise training protocol. Subjects performed three sessions of exercise per week consisted of either three supervised combined aerobic and resistance circuit training sessions or two supervised circuit training sessions in addition to one home exercise training session per week, monitored for compliance (CAD, UTHC, THC). Circuit training sessions were performed at the Cardiac Gymnasium, Royal Perth Hospital, with the focus on the large muscles of the lower limbs. Upper body exercises did not involve the forearm, and the subjects were instructed to avoid hand gripping. They were also instructed on correct lifting techniques to avoid the Valsalva maneuver.

The 8-wk “circuit” training protocol involved a combination of resistance training, cycle ergometry, and treadmill walking. The resistance exercises (listed above) were alternated with cycle stations at a work-to-rest ratio of 45:15 s. Subjects performed one lift every 3 s, completing 15 lifts in the 45-s work period. At completion of the circuit, subjects performed an additional 5 min of treadmill walking. Training intensity and duration were progressively increased during the first 2–3 wk, as tolerated. Resistance intensity commenced at 55% of pretraining one repetition maximum and increased to 65% at week 4. Cycling and treadmill walking intensities were initially 70% of peak heart rate, determined from a pretest graded maximal exercise test, and were increased up to 85% of peak heart rate at week 6.

Home training sessions, where performed, were individually prescribed and involved subjects performing continuous aerobic exercise at 70–85% of peak heart rate for up to 45–60 min. To ensure compliance, sessions were recorded in a diary, and heart rates were recorded by using heart rate monitors (Polar Electro Oy, Kempele, Finland).

Analysis of data. In plethysmographic resistance vessel function studies, FBF responses were initially calculated as a ratio of that in the infused arm to that in the noninfused arm, changes in the ratio being expressed as percent changes from the baseline immediately preceding the drug infusion period (2). FBF results to each drug infusion were then expressed as the area under the curve (AUC) of percent changes in FBF ratio responses to the three doses of the drug. To compare trained and untrained data for all variables, including conduit and resistance vessel responses, Student’s paired t-test or two-way ANOVA were used. To examine relationships between variables at baseline (i.e., pretraining), we calculated Pearson correlation coefficients between all variables and baseline FMD, GTN, ACh, AUC, and SNP AUC, thereby providing correlation coefficients and associated significance levels. Relationships between FMD and ACh and between GTN and SNP were specifically determined. Descriptive data at baseline are reported as means ± SD and other data as means ± SE or, for log-transformed data, as geometric mean and 95% confidence limits. Significance was set at P < 0.05.

RESULTS

The results of exercise training within each group are comprehensively described and discussed in individual papers (26, 42, 43) as are the relationships between changes in cardiovascular risk factor profiles and vascular function (12). The purpose of pooling the data in the present analysis was to provide adequate power to compare conduit and resistance vessel, endothelium-dependent and -independent function both before training, and changes as a result of training. Previous papers do not highlight these correlation analyses.

Relationship between variables before training. Subject characteristics for each group studied are displayed in Table 1. When data from each of the groups were pooled before training, FMD was not significantly correlated with the FBF response to ACh, expressed as area under the dose–response curve (ACh AUC) (r = 0.186, P = 0.231; Fig. 1) or as the effect of the maximum dose (40 μg/min) of ACh (r = 0.082, P = 0.602). Indeed, there were no correlations within subgroups between FMD and ACh AUC (UTHC: r = 0.042 P = 0.908; THC: r = 0.184 P = 0.611; CAD r = −0.370, P = 0.376; T2D: r = −0.353, P = 0.197). There was also no significant correlation between GTN and response to SNP expressed as AUC (r = −0.010, P = 0.951; Fig. 1) or as the highest dose (8 μg/min) (r = −0.023; P = 0.884) and no significant correlations within groups.

Effects of exercise training. The ACh response significantly increased after training (Fig. 2; P = 0.05, 2-way ANOVA), whereas no change was evident in SNP responses. Training significantly increased FMD from 3.4 ± 0.5, to 6.0 ± 0.4% (P < 0.0001), whereas the response to GTN was not altered (14.5 ± 0.8 to 13.7 ± 0.9, P > 0.05; Fig. 3).

Correlations between pooled training-induced changes in endothelium-dependent and -independent conduit and resistance vessel function are depicted in Fig. 4. Although both FMD and ACh responses significantly increased with training, there were no statistically significant correlations between changes in conduit and resistance vessel endothelium-dependent function when the groups were pooled (FMD vs. ACh AUC: r = −0.022, P = 0.890; maximum dose: r = 0.041, P = 0.793) or within the individual subgroups (FMD vs. ACh AUC; UTHC: r = 0.028, P = 0.939; THC: r = −0.070, P = 0.849; CAD: r = −0.497, P = 0.211; T2D: r = 0.057, P = 0.840). Similarly, there were no significant correlations between changes in GTN and SNP responses (SNP AUC vs. GTN: r = −0.211, P = 0.191; maximum dose: r = −0.238, P = 0.129) and no significant correlations within groups, although this is perhaps not surprising because neither GTN nor SNP responses improved either in the group as a whole or within subgroups (26, 42, 43).

DISCUSSION

This is the first paper to examine relationships between changes in resistance and conduit vessel function measurements derived from the same subjects before and after an intervention in humans. We report data from a diverse group of subjects with cardiovascular disease and risk factors who exhibited a broad range of vascular dysfunction at entry to the
Despite this, no correlation existed between conduit and resistance vessel measures of either endothelium-dependent or -independent vasodilator function at entry, and, despite significant improvement in both resistance and conduit vessel function in response to exercise training, no relationship existed between the changes observed in these vessels. These data strongly suggest that the magnitudes of improvements in conduit and resistance vessel function in response to exercise training are unrelated in vivo.

Although this is the first study to report relationships between changes in conduit and resistance vessel function induced by an intervention within subjects, a small number of previous studies have compared strain gauge- and ultrasound-derived measures of resistance and conduit vessel function in humans. Irace et al. (16) reported a significant correlation between FMD and ACh dose-response curves \((r = 0.739, P < 0.001)\) in a study of 10 healthy subjects and 6 patients with obesity or hypertension. Somewhat in contrast, Lind et al. (24) found no correlation between brachial FMD and the FBF response to a single dose of the muscarinic agonist methacholine in 16 patients with cardiovascular disease and 10 healthy controls (methacholine vs. FMD, \(r = -0.03\)), whereas, surprisingly, a highly significant relationship between SNP and GTN responses was reported \((r = 0.70, P < 0.01)\). They concluded that differences in the relative contribution of nitric oxide (NO) to the vasodilation mediated by FMD and methacholine, and the variable contribution of other vasodilators to responses mediated by these stimuli, may have accounted for the lack of association observed. Finally, Eskurza et al. (10), in a study of 44 healthy subjects aged 20–79 yr, reported no relationship between FMD and the peak vasodilator response to ACh (\(r = 0.13, P = 0.51\)), a finding similar to that observed in the present study \((r = 0.041; P = 0.79)\). On the whole, we suggest that the above data, and our present finding of independent changes in vascular function in response to exercise training according to vascular territory, do not support the suggestion that noninvasive conduit vessel measurement can serve as a surrogate for global assessment of endothelial function in vivo (10).
Several explanations exist for the lack of association between conduit and resistance vessel responses observed to exercise training in the present study. Eskurza et al. (10) propose that because the response to ACh is only partially NO dependent (30), whereas FMD responses to ischemic stimuli similar to that used in the present study are largely due to NO release (8, 18), differences in the corelease of alternate vaso-dilators may explain the lack of association between ACh and FMD responses. This does not, however, account for the absence of correlation between endothelium-independent dilators in the present study, the response to which is entirely NO dependent. A second possibility relates to the difference in measurement techniques. Plethysmography, the traditionally accepted method for assessment of peripheral blood flow in humans is, however, difficult to validate because derivation of absolute flows necessitates assumptions relating to the consistency of the geometric shape, proportional swelling, and the tissue composition of the forearm along its length. Ultrasonographic measurement of arterial diameter, in contrast, is relatively easy to validate by using phantom arteries, and our laboratory has previously undertaken a comprehensive assessment of the accuracy and reproducibility of our methodology, including automated edge-detection and wall tracking software, which indicates that the resolving power of the system approximates 8 μm (45). Given that exercise training was associated with improvement in both plethysmographic ACh responses and ultrasound FMD assessments in the present study, the lack of association between these changes appears unlikely to be due to differences in measurement techniques.

Finally, the lack of association between resistance and conduit vessel responses in the present study may relate to differences in the physiological mechanisms responsible for exercise training-induced changes in different vascular territories. It is well established that shear stress plays an important role in exercise training-induced changes in vascular endothelial function (29), a conclusion recently endorsed by an elegant in vivo study in patients with coronary disease (15). Given that acute bouts of exercise induce changes in local hemodynamic conditions and shear stress that differ according to branch order of the vascular tree, it is likely that the contribution of this, and other mechanisms responsible for vascular adaptations, differ at distinct loci. Indeed, it has been suggested that exercise training induces structural enlargement of conduit vessels (arteriogenesis) that is dependent on shear stress-mediated NO release and may be an adaptive response that acts to mitigate
the increases in transmural pressure and wall stress brought about by repeated exercise bouts (13, 20, 25, 34, 35, 39, 46). In contrast, microvascular angiogenesis, although endothelium (and vascular endothelial growth factor) dependent, appears to occur primarily in responses to hypoxia rather than shear stress, and NO is not obligatory (25, 34). In addition, evidence is emerging that the contribution of substances such as NO to exercise training-mediated adaptations in vascular structure and function may be vessel caliper dependent, with larger vessels that are exposed to higher shear stress forces possessing greater capacity for NO production (22, 23). Interestingly, given NO is an antiatherogenic molecule, it has long been known that regions of low shear are predisposed to advanced lesion formation (29). Thus the most likely explanations for the lack of association between resistance and conduit vessel responses in the present study probably relate to the likelihood that distinct physiological mechanisms are involved in the modulation of resistance and conduit function in response to exercise training and that, furthermore, the plethysmographic and ultrasound methods interrogate different effector pathways in the vessel wall.

There are several potential limitations of the present study. The subjects studied exhibited a heterogeneous cross section of cardiovascular diseases and risk factors, although medications were not altered in any subject across the period of study. In studies using correlation analysis, it might be argued that detection of relationships is more likely when a wide variation in the vessel wall.

In summary, no association was observed between the com-


