Exercise training improves conduit vessel function in patients with coronary artery disease

Jennifer H. Walsh, William Bilsborough, Andrew Maiorana, Matthew Best, Gerard J. O’Driscoll, Roger R. Taylor, and Daniel J. Green. Exercise training improves conduit vessel function in patients with coronary artery disease. J Appl Physiol 95: 20–25, 2003; 10.1152/japplphysiol.00012.2003.—It is well established that endothelial dysfunction is present in coronary artery disease (CAD), although few studies have determined the effect of training on peripheral conduit vessel function in patients with CAD. A randomized, crossover design determined the effect of 8 wk of predominantly lower limb, combined aerobic and resistance training, in 10 patients with treated CAD. Endothelium-dependent dilation of the brachial artery was determined, by using high-resolution vascular ultrasonography, from flow-mediated vasodilation (FMD) after ischemia. Endothelium-independent vasodilation was measured after administration of glyceryl trinitrate (GTN). Baseline function was compared with that of 10 control subjects. Compared with matched healthy control subjects, FMD and GTN responses were significantly impaired in the untrained CAD patients [3.0 ± 0.8 (SE) vs. 5.8 ± 0.8% and 14.5 ± 1.9 vs. 20.4 ± 1.5%, respectively; both P < 0.05]. Training significantly improved FMD in the CAD patients (from 3.0 ± 0.8 to 5.7 ± 1.1%; P < 0.05) but not responsiveness to GTN (14.5 ± 1.9 vs. 12.1 ± 1.4%; P = not significant). Exercise training improves endothelium-dependent conduit vessel dilation in subjects with CAD, and the effect, evident in the brachial artery, appears to be generalized rather than limited to vessels of exercising muscle beds. These results provide evidence for the benefit of exercise training, as an adjunct to routine therapy, in patients with a history of CAD.

endothelium; blood flow; nitric oxide; ultrasound

IN ADDITION TO REGULATION of vascular tone, the vascular endothelium influences the progression of atherosclerosis via anticoagulant, anti-inflammatory, and vascular remodeling properties (28). Several studies have indicated that subjects with cardiovascular disease or risk factors exhibit impaired endothelium-dependent vasomotor responses (2, 5, 7, 29, 33) and attenuated vascular NO bioactivity. Furthermore, interventions such as lipid-lowering and angiotensin-converting enzyme (ACE) inhibitor therapy, which improve cardiovascular mortality and morbidity, are also associated with improved NO-mediated vascular function (17, 25, 26). The clinical relevance of endothelial dysfunction has been further highlighted by recent studies indicating that endothelial dysfunction is an independent predictor of cardiac events in patients with and without established coronary artery disease (CAD) (24, 34).

Regular physical exercise improves endothelium-dependent vasodilation in a number of populations, including those with heart failure (11, 18, 21), Type 2 diabetes (20), and hypertension (13). Animal studies indicate that changes in blood flow and, therefore, endothelial shear stress during repetitive exercise result in upregulation of NO synthase expression (30) and enhanced endothelium-mediated relaxation (32). More recent evidence suggests that exercise training not only improves vascular function in the exercising musculature but also induces generalized improvement in endothelial function (16, 18, 20, 21), possibly as a result of hemodynamic and shear stress-mediated changes associated with exercise (10).

Exercise training for patients with stable CAD is now generally accepted as a nonpharmacological intervention to improve functional capacity and provide risk factor modification, although the mechanisms responsible for the salutary effects of exercise are not fully understood (15, 31). Improvement in endothelial and vascular function may explain, in part, the beneficial effects of exercise training on functional capacity and cardiovascular outcomes. Despite its importance, few studies have examined the effect of exercise training on endothelial function in patients with CAD; one study found coronary endothelium-dependent dilation to be improved (12), whereas another found a 10-wk program of leg exercise to increase flow-mediated dilation (FMD) significantly in the posterior tibial artery but insignificantly in the brachial artery (9). In view of this and our laboratory’s previous study finding FMD to be increased in the brachial artery by lower body exercise.
training (20), we studied a group of patients with stable CAD.

METHODS

Subjects. Ten men with a history of CAD were recruited from hospital clinics or via public advertisement. To be eligible, patients must have had CAD requiring surgical (Coronary artery bypass graft) or nonsurgical revascularization (Percutaneous transluminal coronary angioplasty). The numbers having these interventions or having previous myocardial infarction are shown in Table 1. Patients who had undergone surgery or coronary intervention or had myocardial infarction during the previous 3 mo were excluded, as were those who had valvular heart disease, a left ventricular ejection fraction <40%, chronic obstructive lung disease, or renal or hepatic dysfunction. Patients were also excluded if they were current smokers; currently had diabetes, asthma, hypertension (systolic blood pressure >160 mmHg or diastolic blood pressure >90 mmHg), or hypercholesterolemia (total cholesterol >6.0 mmol/l or low-density lipoprotein cholesterol >4.0 mmol/l); or performed more than two sessions of light-to-moderate exercise per week. All were taking aspirin, four took 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor (statin) therapy, seven took an ACE inhibitor, two took a proton pump inhibitor, and one took tor (statin) therapy, seven took lipid profile were not significantly different from the CAD patients at the time of their recruitment. The characteristics of CAD patients and healthy control subjects enrolled in the study are presented in Table 1. The Royal Perth Hospital Ethics Committee approved the protocol, and all subjects gave written, informed consent.

Study design. All subjects underwent baseline assessment, after which CAD patients were randomly assigned to either remain sedentary or exercise train for 8 wk according to the protocol outlined below. Assessments were then repeated, and crossover occurred with final assessments made 16 wk after entry. In previous studies with a similar 8-wk exercise program, such a crossover design has proved satisfactory with no evidence, by subgroup analysis, of persisting effects of exercise in subjects randomized to train first (20, 21). Patients were requested to maintain their normal diet and other lifestyle behaviors for the duration of the study, and this was confirmed with interview and questionnaire.

Assessments of vascular function were conducted in a quiet, temperature-controlled laboratory after an 8-h fast, 12-h abstinence from caffeine, and 24-h abstinence from alcohol and exercise. For individual patients, repeat assessments were performed at the same time of day and time of medication use was standardized.

Assessment of peak reactive hyperemia. Measures of peak reactive hyperemic blood flow were performed in eight CAD patients before conduit vessel function assessment. Subjects were positioned with elbows at heart level and hands at a comfortable height to allow forearm venous drainage. Pneumatic cuffs (SC10 and SC5, D. E. Hokanson, Bellevue, WA) and strain gauges (SG 24, Medasonics, Mountain View, CA) were positioned for forearm blood flow measurements. Wrist and upper arm cuffs were connected to rapid inflation devices (E-20 and AG 101, D. E. Hokanson); strain gauges were positioned 8–10 cm distal to the olecranon of each arm. Strain-gauge placement and hand and elbow 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 that blood flow measurements were synchronized with upper arm cuff inflation.

Five minutes after subject preparation was complete, upper arm cuffs were inflated to >200 mmHg for a period of 10 min to provide a stimulus for reactive hyperemic blood flow (RHBFl0) in each forearm. Immediately before upper arm cuff deflation, hand blood flow was occluded by inflation of wrist cuffs to 200 mmHg. Peak vasodilator capacity was taken as the maximal flow after upper arm cuff deflation, in all cases, being within the first 30 s.

A 20-min rest period was observed to allow blood flow to return to baseline before conduit vessel function assessments were performed.

Assessment of conduit vessel function. Patients rested supine with the nondominant arm extended and immobilized with foam supports 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. A rapid inflation and deflation pneumatic cuff was positioned on the brachial arm immediately distal to the olecranon process to provide a stimulus to forearm ischemia. 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 third of the upper arm.

Table 1. Baseline (entry) characteristics of CAD patients and healthy control subjects

<table>
<thead>
<tr>
<th></th>
<th>CAD Patients</th>
<th>Control Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>55 ± 2</td>
<td>54 ± 1</td>
</tr>
<tr>
<td>Previous myocardial infarction, no.</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Previous coronary angioplasty/stent, no.</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Previous coronary artery bypass graft, no.</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Peak oxygen consumption, ml-kg−1·min−1</td>
<td>27.0 ± 1.7</td>
<td></td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>55 ± 2</td>
<td></td>
</tr>
<tr>
<td>Resting systolic blood pressure, mmHg</td>
<td>128 ± 7</td>
<td>132 ± 5</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mmHg</td>
<td>72 ± 4</td>
<td>79 ± 3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.8 ± 1.2</td>
<td>25.7 ± 0.7</td>
</tr>
<tr>
<td>Plasma lipids, mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.3 ± 0.4</td>
<td>5.1 ± 0.1</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>2.6 ± 0.3</td>
<td>3.0 ± 0.2</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>1.0 ± 0.1</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.4 ± 0.2</td>
<td>2.1 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. Note that all but 1 of the coronary artery disease (CAD) patients were on 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor therapy. No significant differences in baseline variables between CAD patients and control subjects were evident at the time of study.

J Appl Physiol • VOL 95 • JULY 2003 • www.jap.org
When an optimal image was attained, the probe was held stable in a stereotactic clamp and the probe position relative to the radiale was recorded for repeat sessions. Ultrasound parameters were set to optimize longitudinal, B-mode images of the lumen-arterial wall interface.

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

Brachial artery diameters were analyzed at the time of the ECG R wave, that is, at end diastole. The same experienced sonographer performed the analysis 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 2.5% in a crossover design study with only five subjects (36). The mean intraobserver coefficient of variation of repeated measures of FMD when this software is used is 6.7%, which is significantly lower than that for traditional manual methods (36).

Exercise training protocol. Patients attended two supervised combined aerobic and resistance, “circuit” training sessions at the Cardiac Gymnasium, Royal Perth Hospital, and completed one home training session per week. The focus was on the large muscles of the lower limbs. Upper body exercises did not involve hand-gripping or forearm exercise, and patients were instructed on correct lifting techniques and to avoid the Valsalva maneuver.

The 8-wk circuit training protocol involved a combination of resistance training, cycle ergometry and treadmill walking as described in recent publications (19–21). Eight resistance exercises, performed on weight stack machines (Pulsestar, Cheshire, UK), were alternated with eight cycle stations at a work-to-rest ratio of 45:15 s. Therefore, the total time taken to perform one complete circuit was 16 min. Subjects performed 1 lift every 3 s, completing 15 lifts in the 45-s work period. The number of circuits performed gradually increased from one to three complete circuits during the first 2–3 wk, as tolerated. At completion of the circuits, subjects performed an additional 5 min of treadmill walking. Resistance intensity commenced at 55% of pretraining 1 repetition maximum and increased to 65% at week 4. The eight resistance exercises consisted of seated leg press, standing calf raise, left and right hip flexion, pectoral exercise, seated abdominal flexion, shoulder extension, and seated leg flexion. Cycling and treadmill walking intensities were initially 70% of peak heart rate (HRpeak), determined from a prestudy graded maximal exercise test, and were increased up to 85% of HRpeak at week 6.

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

Data analysis. To compare trained and untrained data for all variables, including FMD and GTN responses, Student’s paired t-test was used. To compare the responses of CAD patients and healthy control subjects, an unpaired t-test was used. Data are reported as means ± SE. Significance was accepted at P < 0.05.

RESULTS

Of the 10 CAD patients, 4 were randomized to receive exercise training for the first 8-wk period. All patients completed 16 supervised training sessions and 8 home training sessions, and no adverse events were experienced during the study period.

General training effects. The 8-wk exercise training period significantly improved symptom-limited, maximum cycle ergometer exercise test duration from 991 ± 63 to 1,087 ± 66 s (P < 0.01). However, despite a trend toward improvement, peak oxygen consumption did not significantly change. Cholesterol, triglycerides, fasting blood glucose levels, resting heart rate, and blood pressures were unaltered by training (Table 2).

Peak reactive hyperemic responses. In the CAD patients, RHPB10 was not significantly altered with exercise training in either the dominant (28.4 ± 4.1 vs. 29.4 ± 3.6 ml·100 ml⁻¹·min⁻¹; P > 0.8) or nondominant (33.7 ± 3.5 vs. 38.7 ± 5.0 ml·100 ml⁻¹·min⁻¹; P > 0.2) arm.

Conduit vessel function assessment. Flow- and GTN-mediated dilator responses in patients in the untrained state were compared with those of the healthy, untrained control subjects of similar age. Basal brachial artery diameter was not significantly different between the CAD patients and control subjects (4.2 ± 0.1 vs. 3.9 ± 0.1 mm; P > 0.05). FMD responses were significantly impaired in the CAD patients (3.0 ± 0.8 vs. 5.8 ± 0.8%; P < 0.05) as were GTN responses (14.5 ± 1.9 vs. 20.4 ± 1.5%; P < 0.05; Fig. 1).

In the CAD patients, basal brachial artery diameter was not significantly different in the untrained and trained states (4.2 ± 0.1 vs. 4.1 ± 0.1 mm; P > 0.2). Exercise training significantly increased the FMD response to forearm ischemia (3.0 ± 0.8 to 5.7 ± 1.1%; P < 0.05). Endothelium-independent dilation in response to GTN was not changed (14.5 ± 1.9 vs 12.1 ± 1.4%; P > 0.21; Fig. 2). In keeping with previous studies involving an 8-wk crossover design (20, 21), the order in which patients trained did not significantly affect responses to training, and FMD in the untrained

Table 2. Characteristics after trained and untrained periods

<table>
<thead>
<tr>
<th></th>
<th>Untrained</th>
<th>Trained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise test duration, s</td>
<td>991 ± 63</td>
<td>1,087 ± 66*</td>
</tr>
<tr>
<td>Peak oxygen consumption, ml·kg⁻¹·min⁻¹</td>
<td>26.6 ± 1.8</td>
<td>28.0 ± 1.9</td>
</tr>
<tr>
<td>Resting systolic blood pressure, mmHg</td>
<td>126 ± 6</td>
<td>121 ± 6</td>
</tr>
<tr>
<td>Resting diastolic blood pressure, mmHg</td>
<td>70 ± 3</td>
<td>70 ± 4</td>
</tr>
<tr>
<td>Resting heart rate, beats/min</td>
<td>56 ± 3</td>
<td>52 ± 3</td>
</tr>
<tr>
<td>Plasma lipids, mmol/l</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>4.5 ± 0.2</td>
<td>4.5 ± 0.3</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>2.8 ± 0.2</td>
<td>2.7 ± 0.2</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>1.5 ± 0.2</td>
<td>1.6 ± 0.2</td>
</tr>
<tr>
<td>Fasting blood glucose, mmol/l</td>
<td>4.9 ± 0.2</td>
<td>5.2 ± 0.2</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>88.4 ± 5.3</td>
<td>88.6 ± 5.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. *P < .01.

J Appl Physiol • VOL 95 • JULY 2003 • www.jap.org
state was not different between those who trained first or second.

**DISCUSSION**

Our randomized crossover design study found FMD of the brachial artery improved after 8 wk of combined aerobic and resistance exercise training in patients with stable CAD, indicating enhanced endothelium-dependent vascular function in the brachial artery. Because endothelial dysfunction appears to be an integral component of atherogenesis (28), and in light of recent studies showing endothelial dysfunction to be an independent predictor of future cardiac events in patients with and without established CAD (24, 34), these findings are of likely relevance in the management of patients with CAD. The exercise program was supervised, outpatient gymnasium based, and designed to largely exclude upper limb exercise, but a similar program of thrice weekly exercise could be easily adapted for home implementation in suitable stable patients.

The present study does not specifically address the mechanisms responsible for the improvement in endothelium-dependent vasodilation, which remain speculative. Early studies found that an increase in blood flow and vessel wall shear stress induces an increase in the endothelial production of vasodilator compounds (23). Animal studies have found that exercise training is associated with an increase in vascular NO production (30, 32) and upregulation of NO synthase expression (30), again attributable to repeated episodes of vascular wall shear stress. Furthermore, Green et al. (10) recently demonstrated augmented NO bioactivity in the upper limb vessels during an acute bout of lower limb exercise in normal volunteers. Hence, our data showing an increase in FMD in a conduit artery of a nontrained muscle bed are consistent with many previous studies and concur with the thesis that recurrent augmentation of vessel wall shear stress, as a consequence of repeated, exercise-induced hemodynamic changes, results in a generalized increase in NO bioactivity throughout the vasculature (16, 18, 20, 21). It is, however, possible that this results not only from upregulation of NO production but also from other phenomenon such as the quenching of NO by superoxide radicals (1).

Our findings are consistent with previous studies in healthy subjects (4) and in subjects with heart failure (11, 18), diabetes (20), and hypertension (13), which demonstrated enhanced endothelium-dependent dilator function, without improvement in endothelium-dependent...
independent dilator function, after a period of exercise training. They are also consistent with those of Hambrecht et al. (12), who showed that 4 wk of 10-min daily cycle training performed six times per day improved coronary endothelium-mediated dilator function, but not endothelium-independent dilation, in patients with CAD. The conclusions of Gokce et al. (9) are at minor variance with ours. These authors studied the effect of a 10-wk period of treadmill or stationary bicycle exercise in CAD patients having similar demographics to our group, but they compared the results with a CAD nonexercise group. FMD increased significantly in the posterior tibial artery, by a mean of 2.0%, whereas the 1.9% increase in the brachial artery did not reach significance. The initial FMD in our subjects was substantially lower, consistent with greater depression of endothelial function, and the improvement was larger but the apparent differences may also be methodological. As mentioned above, we consider the evidence supports a systemic vascular effect of exercise to be substantial.

We did not submit the normal, control subjects, used for baseline comparative purposes, to an exercise program because of the previous observations in such subjects (4). Compared with the healthy subjects, endothelium-independent dilator function, assessed by the response to GTN administration, was impaired in the CAD patients before training. This is consistent with previous observations that subjects with early vascular disease tend to exhibit endothelial but not vascular smooth muscle dysfunction (3, 6, 33, 35), whereas those with more advanced vascular disease may manifest abnormality in both endothelial and smooth muscle function (8, 11, 37). The lack of improvement in smooth muscle function after 8 wk of training in CAD patients is also consistent with previous observations (11, 12, 20) and with our finding that RHBF10, an index of vascular structure (27), was unaltered by training. These observations support the concept that, whereas enhanced endothelium-mediated vasodilation can result from short-term training and serve to buffer shear stress during early exercise periods, longer term training may be necessary to stimulate changes in the vessel wall and, hence, improvement in endothelium-independent function or vessel structure (22). At the same time, in this and other studies, the apparent lack of improvement in this aspect of vascular function could depend on the assessment technique. That is, the dose of GTN conventionally administered may have interrogated the upper end of the dose-response curve, and construction of a dose-response relationship could be more revealing.

The order of training did not affect the vascular response in the present study, and there was no difference in untrained data between those who trained first or second. These findings are consistent with previous crossover design studies that suggest that vascular function follows a similar conditioning-deconditioning time course to that of other exercise-induced physiological adaptations (20, 21) and that some, as yet undefined, level of ongoing exercise may be necessary to maintain training-induced vascular function gains.

The possibility that differing drug regimes may have affected vascular function cannot be excluded. However, the medications were typical of those taken by patients with CAD, and no changes were made throughout the study period. Therefore, the results are likely to be widely applicable to CAD patients on standard therapies. Another possible limitation of the study relates to the training program used: predominantly lower limb and gymnasium based. However, its elements were generic and could be easily modified to suit home- or community-based environments, though it is possible that different training intensities, frequencies, or modalities may elicit other results and that a longer term program would seem necessary for sustained response. The propriety of a randomized sequence of exercise and nonexercise periods also arises. However, with a relatively short-duration exercise training program such as we used, our laboratory has previously found no significant carryover effect of exercise in those trained first (20, 21), as was also the case in this study. Furthermore, if there were any such effect, it would only serve to minimize the effect size observed using a cross-over design.

The findings of this study provide further evidence for the beneficial effect of an exercise training program on endothelium-dependent vascular function in patients with stable CAD undergoing routine management. Furthermore, the benefit is not limited to the vasculature of the trained muscle bed, because changes in the brachial artery were observed as a result of lower limb exercise. Exercise training-mediated improvement in vascular endothelial function may, in part, explain the cardiovascular mortality and morbidity benefits attributed to exercise in the CAD population.

This study was supported by National Health and Medical Research Council of Australia Project Grant 211997.

REFERENCES


