COMPARISON OF RESISTANCE AND CONDUIT VESSEL NITRIC OXIDE-MEDIATED VASCULAR FUNCTION IN VIVO: EFFECTS OF EXERCISE TRAINING

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ABSTRACT

Daniel J Green, Jennifer H Walsh, Andrew Maiorana, Valerie Burke, Roger R Taylor, J Gerard O'Driscoll. Comparison of resistance and conduit vessel nitric oxide-mediated vascular function in vivo: Effects of exercise training. – Exercise training improves vascular function in subjects with cardiovascular disease and risk factors but there is mounting evidence 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 (GTN) administration. Resistance vessel endothelium-dependent and –independent function were assessed using intra-brachial administration of acetylcholine (ACh) and nitroprusside (SNP). Randomised cross-over studies of 8 weeks 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 NO-mediated vascular function in both conduit and resistance vessels, the magnitude of these improvements are unrelated.
KEYWORDS
EXERCISE, ACETYLCOLINE, FLOW-MEDIATED DILATION, RESISTANCE VESSEL, CONDUIT ARTERY

ABBREVIATIONS
FMD: flow-mediated dilatation
SNP: sodium nitroprusside
T2D: Type 2 diabetes subjects
UTHC: Untreated hypercholesterolaemia subjects
THC: Treated hypercholesterolaemia subjects
ACh: acetylcholine
GTN: glyceryl trinitrate
CAD: Coronary artery disease subjects
INTRODUCTION

The endothelium, strategically located at the interface between the circulating blood and vascular wall, homeostatically regulates vascular tone, 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 which 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 factor assessment (3, 40) and may represent a potential barometer of cardiovascular risk (41).

The two most common methods of assessing endothelial dysfunction in vivo involve construction of blood flow response curves to local intra-arterial infusion of agents which stimulate endothelium-dependent and –independent vasodilation, and measurement of shear stress and glyceryl trinitrate (GTN)-mediated large artery vasodilation using high-resolution ultrasound (11). The former method typically involves strain-gauge plethysmographic measurement of forearm blood flow responses to intra-brachial drug administration, most often to acetylcholine (ACh) and nitroprusside (SNP). The latter non-invasive 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) whilst 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 have 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 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.

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 >6.5mmol.l⁻¹ and/or LDL >4.0mmol.l⁻¹ and none were taking any medication. Treated hypercholesterolemic subjects (THC; n = 10) were taking an HMG-CoA reductase inhibitor in stable dose for at least 3 months (8 on atorvastatin, 1 simvastatin and 1 cerivastatin) and had documentation that total cholesterol was >6.5mmol.l⁻¹ and/or LDL >4.0mmol.l⁻¹ prior to treatment. Four THC subjects were also taking aspirin; 1 amlodipine (subject was normotensive for study duration) and 1 constant dose oestradiol. Coronary artery disease subjects (CAD; n = 8) had CAD requiring surgical (coronary artery bypass grafting) or non-surgical revascularisation (percutaneous transluminal coronary angioplasty). All were taking aspirin and were on HMG-CoA reductase inhibitor (statin) therapy, 7 β-blocking therapy, 5 an angiotensin-converting enzyme (ACE) inhibitor, 2 a proton pump inhibitor, and one each 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, 5 were taking an ACE inhibitor; 2 were on statin therapy and 2 were taking aspirin. None had evidence of micro- or macro-
vascular 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; hypertensive (resting BP >160/90 mmHg); hypercholesterolemic (total cholesterol >6.0mmol.l\(^{-1}\) or LDL >4.0mmol.l\(^{-1}\); except the UTHC subgroup); diabetic (except the T2D group); asthmatic; displayed evidence of coronary or valvular heart disease from history, examination and exercise electrocardiography (except the CAD subgroup); performed >2 sessions of light-moderate exercise per week; or were unable to exercise due to physical limitations. No subject had undergone a surgical procedure within the 3 months 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). Following preliminary screening and baseline assessments, subjects were randomly assigned to remain sedentary or perform exercise training for 8-week periods, followed by cross-over. 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 with 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 hours, abstained from alcohol and caffeine for 12 hours and did not perform any exercise for 24 hours before assessments.

Assessment of Conduit Vessel Function

Resting supine, the non-dominant arm was extended and immobilized with foam supports and positioned at an angle of approximately 80° from the torso. Heart rate (HR) was continuously monitored with a 3-lead electrocardiograph (ECG) and mean arterial pressure (MAP) was determined from an automated sphygmomanometer (Dinamap 8100, Critikon; Florida, USA) on the contralateral arm. Resting HR and BP measures were recorded after 30 min of supine rest in all subjects.

A rapid inflation/deflation pneumatic cuff was then positioned on the imaged arm immediately distal to the olecranon process to provide a stimulus to forearm ischemia (6). A 10MHz multi-frequency linear array probe attached to a high-resolution ultrasound machine (Aspen, Acuson; California, USA) was used to image the brachial artery in the distal third of the upper arm. When an optimal image was attained, the probe was held stable in a stereotactic clamp. Ultrasound parameters were set to optimise longitudinal, B-mode images of the lumen/arterial wall interface.

Following 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 200mmHg for 5 min. Images were recorded 30 sec before cuff deflation and for 2 min after deflation. Following 10 min rest, to allow arterial diameter to return to baseline, another 2 min baseline recording was made before a sublingual 400µg spray dose of glyceryl trinitrate (GTN) with images recorded for a further 5 min.
Brachial artery diameters were analysed using custom designed edge-detection and wall-tracking software which minimises investigator bias and has the power to detect an absolute change in FMD of 2% in a cross-over design study with only 6 subjects (45). Briefly, an edge-detection algorithm averages >300 diameter measurements per frame, with 20-30 frames assessed per sec. Those average diameter measures which coincide with the ECG R wave (also auto-detected), that is, occurring at end-diastole, were subsequently analysed using a third order polynomial curve (45). FMD and GTN responses were then calculated from the peak value derived from this polynomial curve, 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).

Assessment of Resistance Vessel Function

While lying supine, a 20-gauge cannula (Arrow; Pennsylvania, USA) was inserted into the brachial artery of the non-dominant arm, under local anesthesia with <2ml of 1% lignocaine, to infuse vasoactive agents and sterile saline, and for blood sampling and measurement of intra-arterial pressure. Subjects were then 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; Washington, USA) and strain-gauges (SG 24, Medasonics; Fremont, California) were positioned for forearm blood flow (FBF) measurements. Wrist and upper arm cuffs were connected to rapid inflation devices (E-20 and AG 101, Hokanson); strain-gauges were positioned 8-10cm distal to the olecranon process 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 75Hz, which was displayed in real time. A software program controlled cuff inflation/deflation as well as data acquisition, storage and display to ensure blood flow measurements were synchronised with upper arm cuff inflation.
Arterial pressure was monitored continuously with a Hewlett Packard 78353A (Idaho, USA) monitoring system. Acetylcholine (ACh, Miochol - Ciba Vision; New South Wales, Australia) was infused at 10, 20 and 40 \( \mu \text{g} \cdot \text{min}^{-1} \), each for 3 min, and sodium nitroprusside (SNP, David Bull Laboratories; Victoria, Australia) at 2, 4 and 8 \( \mu \text{g} \cdot \text{min}^{-1} \), each for 3 min using a constant-rate infusion pump (IVAC 770, IVAC; California, USA). All solutions were prepared aseptically immediately prior to infusion.

The study protocol was identical for each subject. Baseline measurements were made 20 min after cannulation. Blood flow measurements were made after inflating the wrist cuffs to 200mmHg, to exclude the hands from the circulation, and by rapidly inflating the upper arm cuffs to 45mmHg, to occlude venous flow, for 10 sec out of every 15 sec during baseline and drug infusion periods. For each data collection period, the last 5 measurements of FBF were averaged to give a representative flow for that period. There was a minimum of 10 min rest between ACh and SNP infusions.

**Exercise Training Protocol**

Subjects performed 3 sessions of exercise per week comprised of either 3 supervised combined aerobic and resistance circuit training sessions or 2 supervised circuit training sessions in addition to 1 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 subjects were instructed to avoid hand gripping. They were also instructed on correct lifting techniques to avoid the Valsalva maneuver.
The 8-week '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 sec. Subjects performed one lift every 3 sec, completing 15 lifts in the 45 sec 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 to 3 weeks, as tolerated. Resistance intensity commenced at 55% of pre-training 1 repetition maximum (1RM) and increased to 65% at week 4. Cycling and treadmill walking intensities were initially 70% of HR\textsubscript{peak}, determined from a pre-study graded maximal exercise test, and were increased up to 85% of HR\textsubscript{peak} at week 6.

Home training sessions, where performed, were individually prescribed and involved subjects performing continuous aerobic exercise at 70-85% HR\textsubscript{max} for up to 45-60 min. To ensure compliance, sessions were recorded in a diary and heart rates were recorded using Polar 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 non-infused arm, changes in the ratio being expressed as percentage 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 percentage changes in FBF ratio responses to the 3 doses of the drug. To compare trained and untrained data for all variables, including conduit and resistance vessel responses, Student's paired \textit{t} test or 2-way ANOVA were used. To examine relationships between variables at baseline (i.e. pre-training), we calculated Pearson correlation coefficients between all variables and baseline FMD, GTN, AUC\textsubscript{ACh} and AUC\textsubscript{SNP}, thereby providing correlation coefficients and associated significance levels.
FMD and ACh, and 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 an 95% confidence limits (CL). 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 prior to training and changes as a result of training. Previous papers do not highlight these correlation analyses.

**Relationship Between Variables Prior to Training**

Subject characteristics for each group studied are displayed in Table 1. When data from each of the groups were pooled prior to training, FMD was not significantly correlated with the FBF response to ACh, expressed as area under the dose-response curve (ACh AUC) ($r = 0.186; P = 0.231$, Figure 1) or as the effect of the maximum dose (40 $\mu$g.min$^{-1}$) of ACh ($r = 0.082; P = 0.602$). Indeed there were no correlations within groups between FMD and AChAUC; 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 ($r = -0.010; P = 0.951$, Figure 1) or as the highest dose (8 $\mu$g.min$^{-1}$) ($r = -0.023; P = 0.884$) and no significant correlations within groups.

**Effects of Exercise Training**

The ACh response to training significantly increased following training (Figure 2, $P = 0.05$, 2-Way ANOVA) whilst no change was evident in SNP responses. Training significantly increased FMD from
3.4 ± 0.5 to 6.0 ± 0.4% ($P < 0.0001$), while the response to GTN was not altered (14.5 ± 0.8 to 13.7 ± 0.9%, $P > 0.05$, Figure 3).

Correlations between pooled training-induced changes in endothelium-dependent and –independent, conduit and resistance vessel function are depicted in Figure 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 AUC$ACh$: $r = -0.022$; $P = 0.890$; maximum dose $r = 0.041$; $P = 0.793$) or within the individual sub-groups (FMD vs $AChAUC$: 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 (AUC$SNP$ vs GTN: $r = -0.211$; $P = 0.191$; maximum dose $n = 40$; $r = -0.238$; $P = 0.129$) and no significant correlations within groups, although this is perhaps not surprising as neither GTN or SNP responses improved either in the group as a whole or within sub-groups (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 study. 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 magnitude 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. 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 (16). Somewhat in contrast, Lind et al. (24) found no correlation between brachial FMD and the forearm blood flow response to a single dose of the muscarinic agonist methacholine in 16 patients with cardiovascular disease and 10 healthy controls (MCh vs FMD, $r = -0.03$) whilst, 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 NO to the vasodilation mediated by FMD and MCh, 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 years, 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 non-invasive 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. propose that because the response to ACh is only partially NO-dependent (30), whilst FMD responses to ischemic stimuli similar to that
used in the present study are largely due to NO release (8, 18), differences in the co-release of alternate vasodilators 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 as 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 using phantom arteries and we have 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 8µm (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 which 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) which is dependent upon
shear stress mediated nitric oxide (NO) release and may be an adaptive response which 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, whilst endothelium(and VEGF)-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 caliber dependent, with larger vessels which 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 exists in baseline characteristics. Another possible limitation relates to the power of the study. With 43 subjects, power analysis indicates that, assuming a two-tailed 5% test, this number was sufficient to detect a significant correlation of 0.4 with 80% power (19). It is notable that previous studies which have reported significant correlations between conduit and resistance vessel function (16, 24) have both studied 16 patients, whereas the present study (n = 43) and that of Eskurza et al. (10) (n = 44) were undertaken in larger cohorts. There is of course a tendency for correlations to be biased by outlying data in studies of
smaller sample size. It is also possible that a longer period of training or a different training protocol may have revealed significant correlations, particularly if the time-course and magnitude of adaptations differs between vessel beds. This is an interesting hypothesis which deserves further investigation, but both conduit and resistance vessel endothelium-dependent function significantly improved in the present study despite the absence of correlation between these changes. Finally, we did not study normal healthy subjects and our conclusions are limited to subjects with cardiovascular disease in whom endothelial function improved with training.

In summary, no association was observed between the commonly used methods of strain-gauge plethysmography and high resolution ultrasound in the present study and we have shown for the first time that changes in conduit and resistance vessel function in response to exercise training are not correlated. This data adds further support to the evolving hypothesis that the mechanisms responsible for exercise training induced adaptations in the vasculature differ according to the vascular territories involved.
ACKNOWLEDGEMENTS

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**Table 1.** Baseline characteristics (mean ± SD) of untreated and treated hypercholesterolemic, CAD and type 2 diabetic patients 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>
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<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>
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<td>BMI (kg·m⁻²)</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>
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<td>Waist:Hip (%)</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>
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<tr>
<td>Total Chol (mmol L⁻¹)</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 Chol (mmol L⁻¹)</td>
<td>4.4 ± 0.5</td>
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<td>2.4 ± 0.6</td>
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<tr>
<td>HDL Chol (mmol L⁻¹)</td>
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<tr>
<td>Blood glucose (mmol L⁻¹)</td>
<td>5.1 ± 0.3</td>
<td>5.1 ± 0.4</td>
<td>5.0 ± 0.8</td>
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<td>Glycated hemoglobin (%)</td>
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<td>SBP (mmHg)</td>
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HC = hypercholesterolemia, CAD = coronary artery disease.
FIGURE LEGENDS:

FIG. 1. Relationship (top panel) between flow mediated dilation (FMD) and area under the dose-response curve for acetylcholine (ACh) and, (lower panel) glyceryl trinitrate (GTN) mediated vasodilation and area under the dose-response curve for sodium nitroprusside (SNP) at entry to the study. Symbols represent relationships evident within different groups studied; ■ medicated hypercholesterolaemics, ○ unmedicated hypercholesterolaemics, ▲ type 2 diabetic and ◊ coronary artery disease patients. When all subjects were pooled, FMD was not significantly correlated with the ACh (r = 0.186; P = 0.231) and GTN was not significantly correlated with SNP (r = -0.010; P = 0.951). There were also no significant correlations within groups. These data indicate that no relationship exists between conduit and resistance vessel measures of endothelium-dependent and –independent vasodilator function in a diverse group of subjects with cardiovascular disease and risk factors.

FIG. 2. Changes in resistance vessel, endothelium-dependent and –independent, vasodilator function in response to exercise training. Training significantly enhanced endothelium-dependent, acetylcholine (ACh)-mediated function (P = 0.05) whilst no change was evident in endothelium-independent sodium nitroprusside (SNP)-mediated responses.
FIG. 3. Changes in conduit vessel, endothelium-dependent and –independent, vasodilator function in response to exercise training. Training significantly enhanced endothelium-dependent, flow-mediated (FMD) dilator function \((P < 0.0001)\), while the endothelium-independent response to glyceryl trinitrate (GTN) was not altered.

FIG. 4. Relationship (top panel) between exercise training-induced changes in flow mediated dilation (FMD) and training-induced changes in the area under the dose-response curve for acetylcholine and, (lower panel) exercise training-induced changes in glyceryl trinitrate (GTN) mediated vasodilation and exercise training-induced changes in area under the dose-response curve for sodium nitroprusside. Symbols represent relationships evident within different groups; ■ medicated hypercholesterolaemics, ○ unmedicated hypercholesterolaemics, ▲ type 2 diabetic and ◊ coronary artery disease patients. When all subjects were pooled, \(\Delta\text{FMD} \) was not significantly correlated with the \(\Delta\text{ACh} \) \((r = -0.022; \ P = 0.890)\) and no significant correlation was evident between \(\Delta\text{GTN} \) and \(\Delta\text{SNP} \) \((r = -0.211; \ P = 0.191)\). There were also no significant correlations within groups. These data indicate no relationship exists between training-induced changes in conduit and resistance vessel endothelium-dependent or -independent function.