Impact of physical training and detraining on endothelium-dependent vasodilation in patients with recent acute myocardial infarction

M. Vona, MD,[a] A. Rossi, MD,[b] P. Capodaglio, MD,[c] S. Rizzo, MD,[a] P. Servi, SE,[a] M. De Marchi, MD,[a] and F. Cobelli, MD[b] *Aosta and Pavia, Italy*

Background There is evidence that aerobic exercise improves endothelial function in healthy subjects as well as in patients with chronic heart failure. However, it is unknown whether this effect occurs in patients with recent myocardial infarction (AMI).

Methods Fifty-two patients with a recent first uncomplicated AMI underwent endothelial function evaluation before and after 3 months of moderate aerobic exercise training. We measured brachial artery vasomotor reactivity using flow-mediated dilation (FMD), a cold pressor (CP) test, and sublingual nitroglycerin. Patients were randomized into 2 groups: 28 patients (G1) underwent training, while 24 patients (G2) served as controls. Brachial artery vasomotor reactivity was reassessed after 1 month of detraining (DT).

Results At baseline the FMD was 1.66% ± 4.11% in G1 and 2.04% ± 3.4% in G2 (P = NS) and vasoconstriction was evident after a CP test. The diameter reduction was −4.1% ± 3.89% in G1 and −4.39% ± 5.67% in G2 (P = NS). At follow-up the FMD had increased to 9.39% ± 4.87% in G1 ($P < .01$) and to 4.4% ± 3.9% in G2 ($P < .01$ vs G1). Vasoconstriction during a CP test was observed only in G2. Endothelium-independent vasodilation was unchanged in both groups. Effort tolerance increased by 32% in G1 patients ($P < .01$ versus G2) and was correlated with FMD change ($R = 0.51$, $P < .01$). After detraining the FMD was significantly reduced in G1 ($P < .01$) and a further vasoconstriction was evident after CP testing.

Conclusions Exercise training improves endothelium-dependent vasodilation in post-AMI patients. This improvement is associated with a significant increase in exercise tolerance. These benefits disappeared after detraining. (Am Heart J 2004;147:1039–46.)

Vascular endothelium plays a major role in the modulation of vascular tone and in cardiovascular homeostasis.[1] Endothelial dysfunction, in particular impaired endothelium-dependent vasodilation, is associated with early atherosclerosis.[2] Recent studies[3,4] have shown that the presence of severe endothelial dysfunction is associated with a less favorable prognosis in patients with coronary atherosclerosis and that endothelial dysfunction seems to be particularly relevant in patients with acute myocardial ischemia.[5] The latter seems to be a partially reversible process,[6] and so research has recently focused on how to improve endothelial function by correcting the main coronary risk factors, changing lifestyle, or prescribing drugs (statins, angiotensin-converting enzyme [ACE] inhibitors, and antioxidants).[7–9] Aerobic physical activity was shown to enhance endothelial function in most of the trials, although the degree of improvement varied according to the type of patients enrolled and the type and intensity of training.[10–17] The studies involved normal subjects,[10,11,13] subjects with coronary risk factors,[12] or heart failure patients.[14–17]

A common finding in these studies was an improvement in the endothelium-dependent response of arteries in different districts (femoral, brachial, or coronary), suggesting that exercise has a nonspecific systemic effect. However, few studies have been performed on patients with coronary artery disease,[18,19] and results on the systemic effects of physical activity are contradictory.[19] There are no data available about the effects of exercise training on endothelial function in patients with recent myocardial infarction. Ischemia certainly aggravates endothelial dysfunction,[5] but the

From the [a]Cardiac Rehabilitation Center, Cardiology, Beauregard Hospital, Aosta, Italy, and the [b]Cardiology Department, and [c]Occupational Rehabilitation Department, Salvatore Maugeri Foundation, IRCCS – Montescano and Pavia, Pavia, Italy.
Submitted March 18, 2003; accepted December 31, 2003.
Reprint requests: Margherita Vona, MD, Riabilitazione Cardiologica, Ospedale Beauregard, 11100 Aosta, Italy.
E-mail: margheritavona@yahoo.it
0002-8703/$ - see front matter

doi:10.1016/j.ahj.2003.12.023

degree of functional impairment after acute myocardial infarction (AMI) and the possible benefits that could be derived from a program of moderate physical activity are not clear. The objectives of the present study were (1) to quantify endothelial dysfunction in patients with recent uncomplicated AMI; (2) to determine the effects of a moderate exercise training program on brachial artery vasomotor reactivity in patients not receiving pharmacologic therapy with statins and/or ACE inhibitors; and (3) to evaluate the effects of detraining 1 month after the completion of regular training.

Methods

Patients

We considered all consecutive male and female patients, aged <70 years, who were referred to a cardiac rehabilitation program between February 1, 2001, and February 1, 2002, after a first uncomplicated AMI (absence of mechanical complications, residual ischemia, left ventricular insufficiency, and severe ventricular and/or supraventricular hyperkinetic arrhythmias) in the previous 3 weeks. Inclusion criteria were: ability to exercise (baseline symptom-free capacity of ≥75 watts on bicycle ergometry), absence of previous cardiovascular events, absence of major modifiable coronary risk factors (ie, normal total and low-density lipoprotein [LDL] cholesterol, no diabetes, no hypertension, nonsmoker or ex-smoker for >10 years), left ventricular ejection fraction ≥45%, and echocardiographic absence of ventricular hypertrophy. We excluded patients taking calcium antagonists, statins, or ACE inhibitors, patients with hemodynamically significant valvular heart disease, cardiopulmonary bypass surgery, chronic lung disease, systemic and/or hematologic illnesses, and hepatic or renal insufficiency (creatinine >2.5 mg/dL). Of the 968 patients referred for the rehabilitation program, 54 (5.6%) met the inclusion criteria. All the patients underwent coronary angiography immediately after hospitalization, and 35% of them underwent coronary angioplasty with stent positioning during or immediately after the acute phase of myocardial infarction. All the patients were being treated with β-blockers and aspirin at the time of investigation.

Protocol

The protocol was approved by the local Ethical Committee. Written informed consent was obtained from all patients before randomization.

The baseline evaluation included the patient's clinical history and examination, resting electrocardiogram (ECG), chest X-rays, blood chemistry (total, high-density lipoprotein [HDL], and LDL cholesterol [Friedwald's formula], triglycerides, baseline and postprandial glycemia, glycate hemoglobin, hematocrit, liver and kidney function tests), transthoracic echocardiogram, and a familiarization ECG stress test. On the following day, brachial vasoreactivity was evaluated and, after a few hours, the ECG stress test was repeated.

Evaluation of arterial vasoreactivity

Endothelial function was assessed using the noninvasive technique proposed by Celermajer[20] and recently revised.[21] Brachial artery reactivity was evaluated by 2-dimensional ultrasonography (Hewlett Packard SONOS 5000) with a linear, high-resolution probe (7.5-10 MHz), fixed in an adjustable swivel arm to maintain an identical position on the forearm during the experiments. All images were taken by the same investigator, who was blind to the patient's study group randomization. The brachial artery was visualized in longitudinal section, 2 to 10 cm from the medial elbow crease. Focusing and gains were optimized for the best axial resolution, in order to visualize the "m" line of the posterior and, possibly, the anterior wall. The image obtained was magnified with a zoom. The flow was monitored by pulsed Doppler with a 65° angle correction relative to the artery and by positioning the 2 mm-volume sample in the center of the vessel. The baseline scan of the vessel was performed after the patient had been lying supine for 10 minutes in a quiet room. The patient was fasting and the last intake of β-blockers had been 24 hours before. The pneumatic cuff under the elbow was then inflated to 260 mm Hg for 5 min. When the cuff was deflated, the baseline flow-mediated dilation (FMD) measurements were repeated during the phase of reactive hyperemia. Images were acquired continuously for 90 seconds after cuff deflation. Fifteen minutes later, after repeat measurements to ensure that arterial diameter had returned to a normal baseline value, a cold pressor (CP) test was performed as follows: the patient's nondominant arm was plunged into a basin filled with ice for 3 minutes; then the flow and the diameter were measured as previously described at 1, 2, and 3 minutes and again during the following 5 minutes. Ten minutes after the CP test, having once again ensured that arterial diameter had returned to normal, the patient received 0.3 mg sublingual nitroglycerin (NTG) to assess endothelium-independent vasodilation, and images were acquired after 5 minutes. The ECG was monitored continuously in all patients. Images were digitalized and recorded on optical disk for off-line analysis.

The day before the baseline experiments the patients underwent a preliminary study to ensure the feasibility of the tests and to familiarize patients with the procedure.

Data analysis

Two experienced evaluators blind to the patient's clinical picture, the stage of study, and to each other's interpretation analyzed the data. Once the images for analysis had been chosen, the boundaries for diameter measurements were identified manually with electronic calipers. Measurements were taken from the center of the "m" line of the anterior wall to the center of the posterior wall in telediastole, incident with the R wave on a continuously recorded electrocardiogram. Each observer analyzed 5 cardiac cycles for each scan and the measurements were averaged. Measurements were performed at baseline, during FMD, and after the CP and NTG tests. Changes in vessel diameter were calculated for each subject as the percentage variation of the arterial diameter under different stimuli compared to the baseline diameter.

Intraobserver variability was assessed by measuring the images stored on the optical disk in the first 10 patients 3

Table I. Study population

	Group 1 (28 pts) (training)		Group 2 (24 pts) (control)		
	No.	**%**	**No.**	**%**	***P***
Males	21	75	19	79	NS
Anterior AMI	6	21.4	4	16.6	NS
Inferior AMI	18	64.3	17	70.8	NS
Non-Q AMI	4	14.3	3	12.5	NS
Coronary angiography					
No stenoses	4	14.3	2	8.3	NS
1 Vessel	13	46.4	13	54.2	NS
2 Vessels	9	32.1	7	29.2	NS
3 Vessels	2	7.1	2	8.3	NS
PTCA	10	36	8	33	NS
Age (y)	56 ± 6		57 ± 8		NS
Ejection fraction (%)	55 ± 7		58 ± 7		NS
CPK peak during AMI (U/L)	1532 ± 1121		1253 ± 539		NS

AMI, Acute myocardial infarction; *PTCA,* percutaneous transluminal coronary angioplasty; *NS,* not significant.

Table II. Metabolic parameters, baseline and follow-up

	Group 1 (training) 28 pts		Group 2 (control) 24 pts	
	Time 0	**Follow-up (3 months)**	**Time 0**	**Follow-up (3 months)**
Total cholesterol (mg/dL)	171 ± 18	183 ± 22*	160 ± 13†	173 ± 19*
HDL cholesterol (mg/dL)	48 ± 12	55 ± 8*‡	46 ± 7	49 ± 8
LDL cholesterol (mg/dL)	94 ± 12	95 ± 9	96 ± 7	99 ± 12
Triglycerides (mg/dL)	149 ± 59	156 ± 34	136 ± 40	140 ± 12
Glycemia	89 ± 9.3	92 ± 8.2	87 ± 7	90 ± 7.9
BMI (kg/m^2)	26.5 ± 2	27 ± 3	25.7 ± 6	26 ± 5

BMI, Body mass index.
*$P < .05$ vs time 0.
†$P < .05$ vs group 1.
‡$P < .05$ vs time 0 and $P < .05$ vs group 2.

months after recording: the mean was 1.3% (range 0%–2.4%). Interobserver variability was 1.9% (range 0.6%–2.7%). In a preliminary study, when these procedures were performed at the same time on 2 different days in 10 healthy volunteers, the average intrasubject variability was not different (1.7%, range 0.4%–2.8%). These findings compare favorably with those in prior reports.[21,22]

Exercise training program

After the baseline evaluation, patients were randomized to receive training (group 1 [G1], 28 patients) or no training (control group [G2], 26 patients). G1 patients underwent moderate aerobic training 3 times a week. Each session included a 10-minute warm-up, 40 minutes of cycling on a cycle ergometer with telemetry monitoring and intensity set at 75% of peak exercise heart rate as measured in the second ECG stress testing, and a 10-minute cool-down. Average heart rate during training was 100 ± 10 beats/minute. Patients were also encouraged to increase their daily physical activity level on the nontraining days by walking more, climbing stairs, and so forth. G2 patients avoided regular physical activity.

Follow-up

All tests were repeated after 3 months and the results compared with those of the baseline tests in both groups. The training program in the G1 patients was stopped at this point. The arterial vasoreactivity and ergometric tests were repeated again after 1 month in both G1 and G2 patients to evaluate the impact of detraining. Pharmacologic therapy remained unchanged throughout the study except in 2 G2 patients, who were prescribed a calcium antagonist and an ACE inhibitor in addition to beta-blockers and aspirin. We excluded these 2 patients, so our complete sample at follow-up was formed of 28 G1 patients and 24 G2 patients.

Statistical analysis

Statistical analysis was performed using SPSS for Windows, V11.1 (SPSS Inc, Chicago, Ill). Data are presented as mean ± SD. Clinical characteristics were compared using Student's unpaired t test or χ^2, when appropriate. Intragroup and intergroup comparisons of the effect of exercise on brachial artery reactivity were performed using analysis of variance for repeated measures, followed by the Tukey post-hoc test.

Linear regression analysis was used to determine the relationship between changes in exercise tolerance and changes in FMD after training and detraining, and between FMD and HDL-cholesterol level changes. A P value < 0.05 was considered statistically significant.

Results

Compliance to training was 88% ± 7%. No adverse events occurred during sessions.

Baseline

No significant differences were found between G1 and G2 patients regarding age, gender, site and dimension of myocardial infarction, or left ventricular ejection fraction (Table I). In line with our inclusion criteria, the sample considered was at low cardiac risk: the majority of the patients had limited extension of coronary artery disease and only 7.1% of the G1 and 8.3% of G2 patients had angiographically demonstrated 3-vessel disease (P = NS). Total cholesterol was slightly but significantly higher in G1 (P = .01), while the other metabolic parameters considered (LDL and HDL cholesterol, triglycerides, and glycemia) and body mass index were not significantly different (Table II). Peak exercise heart rate, blood pressure, rate pressure product, and work rate were similar on initial ECG stress testing (Table III).

Table III. Ergometric testing parameters, baseline and follow-up

	Group 1 (training) 28 pts		Group 2 (control) 24 pts	
	Time 0	Follow-up (3 months)	Time 0	Follow-up (3 months)
HR max (beats/min)	132 ± 8	128 ± 9	129 ± 9	132 ± 7
BP max (mm Hg)	178 ± 14	172 ± 12	174 ± 18	180 ± 22
RPP max	23456 ± 4241	22101 ± 4923	22772 ± 4645	23882 ± 3799
Watts	135 ± 25	175 ± 33*	131 ± 12	125 ± 20
Minutes	13.4 ± 2.7	18 ± 2.8*	13.2 ± 2	13.6 ± 2.5
METs	7.1 ± 2.1	9.2 ± 2.3*	6.9 ± 2.5	7.2 ± 2.7

HR, Heart rate; *BP,* systolic blood pressure; *RPP,* heart rate × systolic blood pressure.
*$P < .001$ versus time 0.

Brachial arterial vasoreactivity

On initial evaluation, the baseline diameter of the brachial artery did not differ significantly between G1 and G2 (4.67 ± 0.66 mm in G1 and 4.71 ± 0.68 mm in G2). After cuff release, the brachial artery diameter increased similarly in both groups: in G1 patients the FMD increased by 1.66% ± 4.11% and in G2 patients by 2.04% ± 3.4%, P = NS) (Figure 1). The CP test induced significant vasoconstriction in G1 and in G2: the diameter reduction was −4.1% ± 3.89% in G1 and −4.39% ± 5.67% in G2 (P = NS) (Figure 1). The maximal vasoconstriction was observed at 1 minute. Nitroglycerin (endothelium-independent vasodilation) induced similar significant ($P < .01$) vasodilation in both groups; the percentage change was 13.5% ± 4.1% in G1 and 13.1% ± 4.6% in G2 (P = NS for intergroup comparison) (Figure 1).

Post-training

All G1 patients and 24 of the 26 G2 patients completed the follow-up. No adverse events occurred in either group during the follow-up.

As shown in Table II, a slight increase in total cholesterol was observed in both groups at 3 months, but no significant differences in LDL cholesterol and triglycerides were found. G1 patients had a significantly greater increase (14.8% ± 5%, $P = .01$) in HDL cholesterol than did the control group ($P = .01$).

At 3 months, functional capacity increased by 32% ± 17% in G1 (from 13.4 ± 2.7 min to 18 ± 2.8 min, $P < .01$ and from 7.1 ± 2.1 to 9.2 ± 2.3 metabolic equivalents [METs], $P < .01$), while it remained unchanged in G2 patients (Table III).

Post-training brachial arterial reactivity

The diameter of the brachial artery at rest did not change significantly between study entry and the 3-month evaluation in either group (4.62 ± 0.57 mm in G1 and 4.64 ± 0.70 mm in G2).

After 3 months there was a significant improvement in brachial artery endothelium-dependent relaxation in trained patients (Figure 1): the FMD increased from 1.66% ± 4.11% to 9.39% ± 4.87% ($P < .01$). The FMD also improved in G2 from 2.04% ± 3.4% to 4.4% ± 3.9% ($P < .05$) but to a lesser extent than in G1 ($P < .01$ for intergroup comparison). Post-training brachial artery diameter after the CP test was unchanged in G1 (Figure 1) (0.5% ± 5.6%, P = NS), while in G2 diameter the reduction persisted (−4.4% ± 6.5%, $P < .01$ vs G1).

No significant variations were observed in endothelium-independent function after 3 months in either group: the percentage changes after the NTG test were 14.1% ± 5.1% in G1 ($P < .01$) and 12.9% ± 5.2% in G2 ($P < .01$) (P = NS for intergroup comparison) (Figure 1).

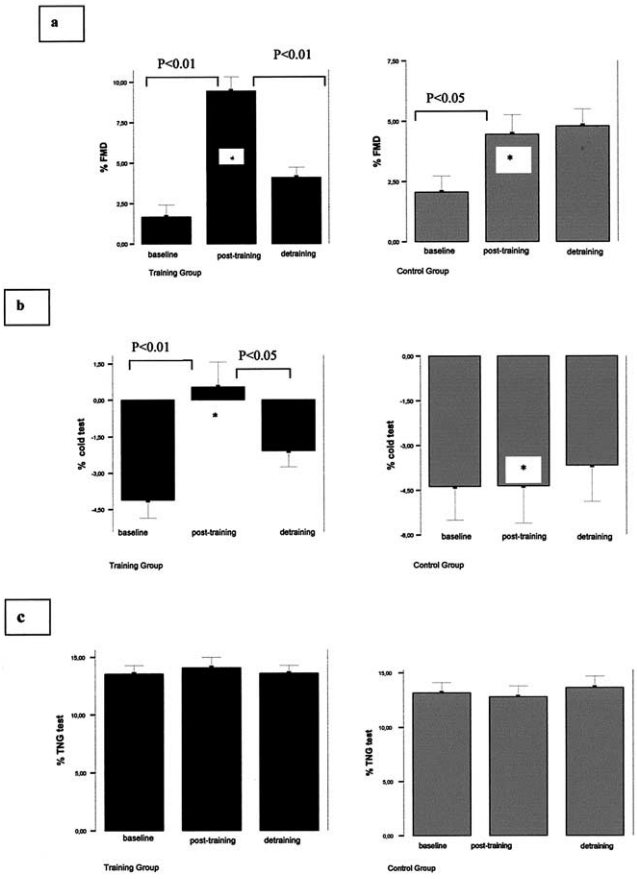
Changes in the FMD were weakly correlated with HDL cholesterol changes ($r^2 = 0.37$, $P = .01$) (Figure 2), and more strongly with changes in work tolerance ($r^2 = 0.51$, $P < .01$) (Figure 3).

Detraining

After 1 month of detraining, work tolerance was reduced by 16% ± 2.3% in G1 (from 18 ± 2.8 to 15.2 ± 2.4 min and from 9.2 ± 2.3 to 7.6 ± 2 METs, $P < .01$). In G1 the brachial artery baseline diameter remained essentially the same (4.67 ± 0.62 mm), but FMD was significantly lower after the detraining than at the end of the training period (4.08% ± 3.38% vs 9.39% ± 4.87%, $P < .01$) (Figure 1). A correlation was observed between changes in FMD and changes in work tolerance ($r^2 = 0.41$, $P < .01$) (Figure 4). Further vasoconstriction was evident after the CP test: the brachial artery diameter in G1 was decreased (−2.1% ± 3.3%, $P < .05$ vs 3 months) (Figure 1). The endothelium-independent vasodilation, however, was unchanged (Figure 1).

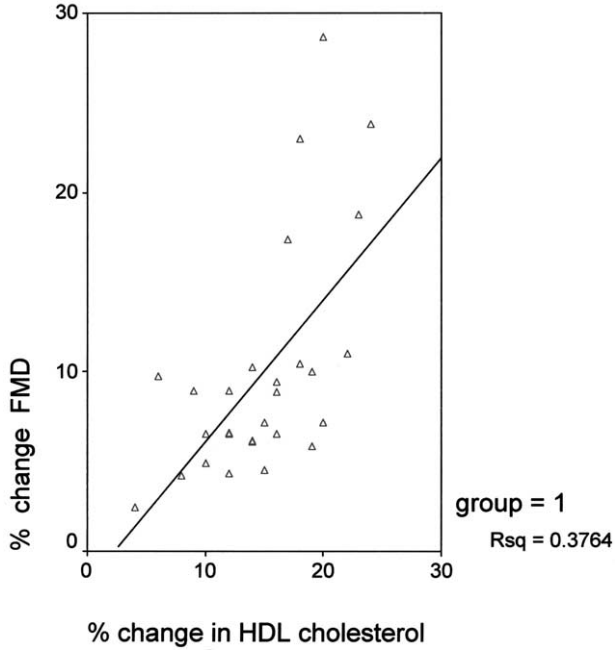
Functional capacity in G2 remained unchanged and no significant variations were observed in brachial ar-

Figure 1



A, Percent change in FMD during brachial reactivity study. The FMD was significantly augmented after 3 months of physical training ($P < .01$ vs baseline and $*P < .01$ for intergroup comparison) and reduced after 1 month of detraining. **B**, Percent change of brachial diameter during CP test. The diameter was significantly augmented after the physical training period ($P < .01$ vs baseline and $*P < .01$ for intergroup comparison) and reduced after 1 month of detraining. **C**, Percent change of brachial diameter after TNG test. No significant differences were observed at any point during the study in training and control groups. Values are mean ± standard error of the mean.

Figure 2



Relation between percent change in FMD and percent change HDL cholesterol.

tery reactivity; in fact, the FMD was 4.6% ± 3.71% (P = NS vs 3 months) and the diameter reduction after CP was −3.6% ± 5.9% (P = NS vs 3 months) (Figure 1).

The FMD% was similar, at 4 months, in both G1 and G2 (Figure 1).

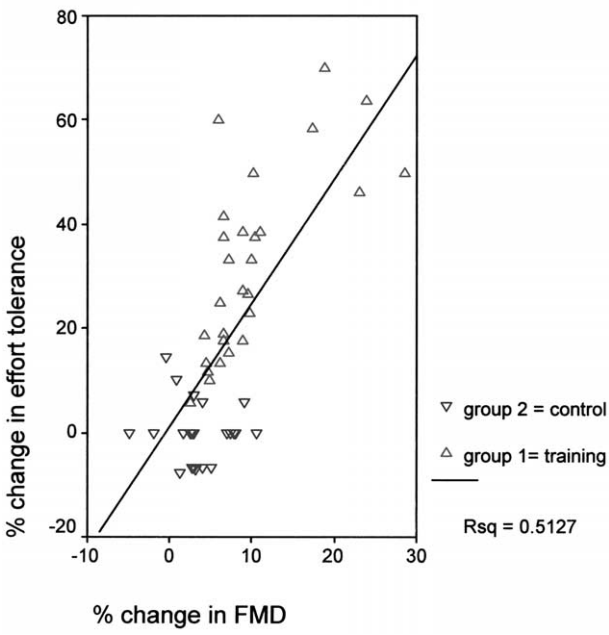
Discussion

Degree of baseline endothelial dysfunction

The first goal of this study was to assess the degree of endothelial dysfunction in a homogeneous group of patients with recent AMI. We measured the FMD in the brachial artery: endothelial dysfunction assessed by this technique is correlated with measures of coronary endothelial dysfunction.[23] Our patients showed severe endothelial dysfunction 3 weeks after a first uncomplicated AMI, similar to the dysfunction that has been observed in patients with unstable angina.[5] These data are in line with the significant vasoconstriction observed at the CP test. To our knowledge this is the first study that has attempted to quantify endothelial dysfunction by assessing FMD and using a CP test, even though experimental data have shown that this dysfunction might be severe in patients with AMI.[24]

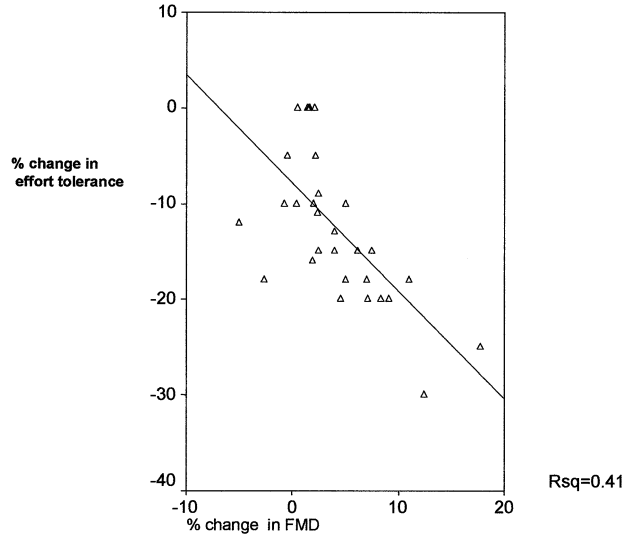
Another aim of our study was to quantify the effect of regular training on endothelial dysfunction. In order to do this, we excluded patients treated with ACE inhibitors and/or statins (both of which have short- and long-term effects on endothelial function), patients with classic risk factors known to affect endothelial function, and patients with left ventricular dysfunction. Only a few (5.6%) of our series of post-AMI patients met the inclusion criteria for enrollment into the study and they had limited extension coronary disease. However, the ultimate result was an extremely homogeneous sample. Since our patients received no treatments other than aspirin and atenolol, the latter not showing significant effects on endothelial function,[25]

Figure 3



Relation between percent change in FMD and percent change in effort tolerance.

Figure 4



Relation between percent change in effort tolerance and percent change in FMD after 1 month of detraining (group 1).

we were able to assess the severity of baseline dysfunction and the entity of spontaneous or training-induced changes over time, unaltered by pharmacologic effects. It seems that in some published studies, treatments affecting endothelial function were suspended only a few hours before investigations.[12] This might have reduced the short-term pharmacologic effects on endothelial function but would not have eliminated chronic and progressive effects that could confound the interpretation of changes induced by other interventions.

The results of the CP test were, in our opinion, particularly significant: they demonstrate that sympathetic stimulation not adequately counteracted by normal endothelial function may cause vasoconstriction, probably representing a direct vasoconstrictive effect on the vascular smooth muscle[26] that is generally directly related to the severity of the disease.[27] Mechanisms postulated to explain the endothelial dysfunction in coronary patients include downregulation of the nitric oxide (NO)-synthase itself[24]and reduced activity of superoxide dismutases, responsible for the reduced degradation of the free radicals that accelerate NO-synthase degradation.[28]

Effects of training on endothelial dysfunction

The main goal of the study was to verify whether post-AMI endothelial dysfunction could be corrected by moderate training. After 3 months of aerobic training, FMD of the brachial artery increased significantly more in the trained group than in the control group. This is in line with previous findings reporting systemic effects induced by training.[17] Furthermore, as observed in heart failure patients,[16] a correlation was found between the FMD increase and enhanced tolerance to effort. It is possible that recent myocardial ischemia, by reducing endothelium-NO availability, impairs the exercise-induced blood flow response and thus reduces exercise capacity.[29] Experimental data from a canine model shows that gastrocnemius muscle ischemia with NO-synthase inhibition was associated with either O_2 limitation or an alteration in the efficiency of muscle contraction.[30] In rats, inhibition of NO-synthase during exercise reduced blood flow to muscles with a high percentage of oxidative fibers.[31] These findings may account, at least partially, for an increased blood flow to oxidative muscles during exercise secondary to training-restored endothelial function and could explain the significant correlation between changes in effort tolerance and changes in FMD noted in the present study. Kuvin et al. reported a similar correlation in patients with suspected coronary artery disease: those with decreased FMD had a significantly lower exercise tolerance than those with a larger FMD.[32] Previous studies[18,19] have verified the effect of training on endothelial function in patients with myocardial ischemia. In the first study, 4 weeks of intense training induced benefits in both epicardial and resis-

tance coronary vessels as demonstrated by the increase in vasomotor responses to acetylcholine and adenosine.[18] In the second, more recent, study[19] the authors observed that, compared to the control group, trained patients had an increase in FMD in the posterior tibial artery but not in the brachial artery, seeming to indicate that training does not have systemic effects. Possible explanations for the discordance with our results include differences in the composition of the population sample, LDL cholesterol levels, treatment, and exercise training intensity. Intense training to obtain a wide body response in endothelial function is a questionable issue: in Hambrecht's study[18] the intensity was very high, but positive systemic responses were also reported with moderate intensity training in normal subjects[10] and in heart failure patients.[17] Our trained patients showed a significant increase in HDL cholesterol. Drug-induced changes in lipid levels have been reported to influence endothelial function.[33] However, in our patients the increase in HDL cholesterol was only weakly correlated with the increase in brachial artery FMD, so the improved endothelial function in the trained patients is unlikely to have been influenced by changes in HDL.

Mechanisms involved in the exercise-induced improvement of endothelial function

Exercise increases shear stress, which is a strong physiological stimulus for NO release:[34] the FMD increase after physical training has been observed in both animals and humans and the mechanism is likely to involve a chronic increase in NO production mediated by an increase in the expression of NO-synthase.[35,36] NO-synthase mrNA is upregulated in cultured endothelial cells exposed to laminar shear stress, and similar observations have been reported in animal studies involving both short- and long-term exercise.[37,38]

Several other mechanisms may be involved in exercise-induced vasodilation. Brachial artery measurements in a porcine model demonstrated that exercise training attenuated the effects of a high-fat diet by enhancing a vasodilator mechanism involving prostacyclin.[39] In another study, after gradual occlusion of the proximal left circumflex coronary artery of female swine, exercise training produced an enhanced relaxation response to bradykinin and adenosine diphosphate in coronary vasculature. This enhancement appeared to involve training-induced increased production of NO as well as increased production or responsiveness to endothelium-derived hyperpolarizing factor.[40]

The lack of vasoconstriction during the CP test observed in our patients after 3 months of training suggests that an exercise-induced improvement in endothelial function can protect against the effects of excessive sympathetic stimuli. It is well known that there is an interaction between NO and norepinephrine, a vasoconstrictor and an index of sympathetic nervous system function.[41]

No changes in endothelium-independent vasodilation were observed in the trained patients: this adds further support to the hypothesis that the changes in vasodilator response are the result of improved endothelial function.

Detraining

Our results obtained after 1 month of detraining agree with the reported findings in heart failure[15] and in diabetic patients[12] 6 weeks and 8 weeks, respectively, after the end of training. Training-induced improvements do not, therefore, appear to last in the long term. The correlation between changes in brachial artery vasodilation and changes in exercise capacity supports the hypothesis that exercise tolerance might partially depend on endothelial function.

Conclusions

The major contributions of the present study are the following: (1) brachial vasoreactivity appears to be severely impaired 3 weeks after an uncomplicated AMI; (2) training significantly contributes to systemic improvement of this endothelial dysfunction, reducing the response to sympathetic stimuli such as the CP test; (3) changes in endothelial function are associated with changes in exercise tolerance; (4) the effects disappear after 1 month of detraining. These findings indicate that regular aerobic training is an effective lifestyle intervention for reversing the loss of endothelium-dependent vasodilation in patients with a recent myocardial infarction, but that the exercise must be continued over time.

References

1. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. Circulation 2002;105:546–9.
2. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046–51.
3. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000;101:948–54.
4. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary artery disease. Circulation 2000;101:1899–1906.
5. Esper RJ, Vilariño J, Cacharrón JL, et al. Impaired endothelial function in patients with rapidly stabilized unstable angina: assessment by noninvasive brachial artery ultrasonography. Clin Cardiol 1999;22:699–703.
6. Celermajer DS. Endothelial dysfunction: does it matter? Is it reversible? J Am Coll Cardiol 1997;30:325–33.

7. Goodfellow J, Bellamy MF, Ramsey MW, et al. Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. J Am Coll Cardiol 2000;35:265–70.
8. Anderson TJ, Elstein E, Haber H, et al. Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF Study). J Am Coll Cardiol 2000;35:60–6.
9. Anderson TJ, Meredith IT, Yeung AC, et al. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. N Engl J Med 1995;332:488–93.
10. Kingwell BA, Sherrard B, Jennings GL, et al. Four weeks of cycle training increase basal production of nitric oxide from the forearm. Am J Physiol 1997;272:H1070–7.
11. Maiorana A, O'Driscoll G, Dembo L, et al. Exercise training, vascular function and functional capacity in middle-aged subjects. Med Sci Sports Exerc 2001;33:2022–8.
12. Maiorana A, O'Driscoll G, Cheetham C, et al. The effect of combined aerobic and resistance exercise training on vascular function in type 2 diabetes. J Am Coll Cardiol 2001;38:860–6.
13. Clarkson P, Montgomery HE, Mullen MJ, et al. Exercise training enhances endothelial function in young men. J Am Coll Cardiol 1999;33:1379–85.
14. Maiorana A, O'Driscoll G, Dembo L, et al. Effect of aerobic and resistance exercise training on vascular function in heart failure. Am J Physiol Heart Circ Physiol 2000;279:H1999–2005.
15. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. Circulation 1996;93:210–4.
16. Hambrecht R, Fiehn E, Weigl C, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation 1998;98:2709–15.
17. Linke A, Schoene N, Gielen S, et al. Endothelial dysfunction in patients with chronic heart failure: systemic effects of lower-limb exercise training. J Am Coll Cardiol 2001;37:392–7.
18. Hambrecht R, Wolf A, Gielen S, et al. Effect of exercise on coronary endothelial function in patients with coronary artery disease. N Engl J Med 2000;342:454–60.
19. Gokce N, Vita AJ, Bader DS, et al. Effect of exercise on upper and lower extremity endothelial function in patients with coronary artery disease. Am J Cardiol 2002;90:124–7.
20. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992;340:1111–5.
21. Corretti MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. J Am Coll Cardiol 2002;39:257–65.
22. Sorensen KE, Celermajer DS, Spiegelhalter DJ, et al. Non-invasive measurements of human endothelium dependent arterial responses: accuracy and reproducibility. Br Heart J 1995;74:247–53.
23. Anderson TJ, Uehata A, Gerhard MD, et al. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol 1995;26:1235–41.
24. Wildhirt SM, Suzuki H, Horstman D, et al. Selective modulation of inducible nitric oxide synthase isozyme in myocardial infarction. Circulation 1997;96:1616–23.
25. Burger W, Hampel C, Kaltenbach M, et al. Effect of atenolol and celiprolol on acetylcholine-induced coronary vasomotion in coronary artery disease. Am J Cardiol 2000;85:172–7.
26. Corretti MC, Plotnik GD, Vogel RA. Correlation of cold pressor and flow-mediated brachial artery diameter responses with the presence of coronary artery disease. Am J Cardiol 1995;75:783–7.
27. Zeiher AM, Drexler H, Wollschlager H, et al. Modulation of coronary vasomotor tone in humans: progressive endothelial dysfunction with different early stages of coronary atherosclerosis. Circulation 1991;83:391–401.
28. Landmesser U, Merten R, Spiekermann S, et al. Vascular extracellular superoxide dismutase activity in patients with coronary artery disease: relation to endothelium-dependent vasodilation. Circulation 2000;101:2264–70.
29. Drexler H. Endothelium as therapeutic target in heart failure. Circulation 1998;98:2652–5.
30. King-VanVlack CE, Mewburn JD, Chapler CK, et al. Endothelial modulation of skeletal muscle blood flow and VO_2 during low- and high intensity contraction. J Appl Physiol 2002;92:462–8.
31. Hirai T, Visneski MD, Kearns KJ, et al. Effect of NO synthase inhibition on the muscular blood flow response to treadmill exercise in rats. J Appl Physiol 1994;77:1288–93.
32. Kuvin JT, Patel AR, Sliney KA, et al. Peripheral vascular endothelial function testing as noninvasive indicator of coronary artery disease. J Am Coll Cardiol 2001;38:1843–9.
33. Kuvin JT, Rämet ME, Patel AR, et al. A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. Am Heart J 2002;144:165–72.
34. Corson MA, James NL, Latta SE, et al. Phosphorylation of endothelial nitric oxide synthase in response to fluid shear stress. Circ Res 1996;79:984–91.
35. Fukai T, Siegfried MR, Ushio-Fukai M, et al. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. J Clin Invest 2000;105:1631–9.
36. Delp MD, Laughlin MH. Time course of enhanced endothelium-mediated dilation in aorta of trained rats. Med Sci Sports Exerc 1997;29:1454–61.
37. Wang J, Wolin MS, Hintze TH. Chronic exercise enhances endothelium-mediated dilation of epicardial coronary arteries in conscious dogs. Circ Res 1993;73:829–38.
38. Sessa WC, Pritchard K, Seyedi N, et al. Chronic exercise in dogs increases coronary vascular nitric oxide production and endothelial cell nitric oxide synthase gene expression. Circ Res 1994;74:349–53.
39. Woodman CR, Turk JR, Williams DP, et al. Exercise training preserves endothelium-dependent relaxation in brachial arteries from hyperlipidemic pigs. J Appl Physiol 2003;94:2017–26.
40. Griffin KL, Laughlin MH, Parker JL. Exercise training improves endothelium-mediated vasorelaxation after chronic coronary occlusion. J Appl Physiol 1999;87:1948–56.
41. Tesfamariam B, Weisbrod RM, Cohen RA. Endothelium inhibits responses of rabbit carotid artery to adrenergic stimulation. Am J Physiol 1987;253:H792–8.