

## EFFECT OF EXERCISE ON CORONARY ENDOTHELIAL FUNCTION IN PATIENTS WITH CORONARY ARTERY DISEASE

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### ABSTRACT

**Background** Studies of the cardioprotective effects of exercise training in patients with coronary artery disease have yielded contradictory results. Exercise training has been associated with improvement in myocardial perfusion even in patients who have progression of coronary atherosclerosis. We therefore conducted a prospective study of the effect of exercise training on endothelial function in patients with coronary artery disease.

**Methods** We randomly assigned 19 patients with coronary endothelial dysfunction, indicated by abnormal acetylcholine-induced vasoconstriction, to an exercise-training group (10 patients) or a control group (9 patients). To reduce confounding, patients with coronary risk factors that could be influenced by exercise training (such as diabetes, hypertension, hypercholesterolemia, and smoking) were excluded. In an initial study and after four weeks, the changes in vascular diameter in response to the intracoronary infusion of increasing doses of acetylcholine (0.072, 0.72, and 7.2  $\mu\text{g}$  per minute) were assessed. The mean peak flow velocity was measured by Doppler velocimetry, and the diameter of epicardial coronary vessels was measured by quantitative coronary angiography.

**Results** In the initial study, the two groups had similar vasoconstrictive responses to acetylcholine. After four weeks of exercise training, coronary-artery constriction in response to acetylcholine at a dose of 7.2  $\mu\text{g}$  per minute was reduced by 54 percent (from a mean [ $\pm$ SE] decrease in the luminal diameter of  $0.41\pm 0.05$  mm in the initial study to a decrease of  $0.19\pm 0.07$  mm at four weeks;  $P<0.05$  for the comparison with the change in the control group). In the exercise-training group, the increases in mean peak flow velocity in response to 0.072, 0.72, and 7.2  $\mu\text{g}$  of acetylcholine per minute were  $12\pm 7$ ,  $36\pm 11$ , and  $78\pm 16$  percent, respectively, in the initial study. After four weeks of exercise, the increases in response to acetylcholine were  $27\pm 7$ ,  $73\pm 19$ , and  $142\pm 28$  percent ( $P<0.01$  for the comparison with the control group). Coronary blood-flow reserve (the ratio of the mean peak flow velocity after adenosine infusion to the resting velocity) increased by 29 percent after four weeks of exercise (from  $2.8\pm 0.2$  in the initial study to  $3.6\pm 0.2$  after four weeks;  $P<0.01$  for the comparison with the control group).

**Conclusions** Exercise training improves endothelium-dependent vasodilatation both in epicardial coronary vessels and in resistance vessels in patients with coronary artery disease. (N Engl J Med 2000; 342:454-60.)

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**T**HE vascular endothelium serves as an important modulator of vasomotor tone and function by synthesizing and releasing nitric oxide.<sup>1</sup> The coronary vascular response to acetylcholine depends on the integrity of the endothelium and the endothelial nitric oxide pathway.<sup>2</sup> Coronary atherosclerosis is associated with progressive impairment of coronary endothelial function. Since endothelium-derived nitric oxide is thought to be necessary to maintain an adequate vascular response to increased blood-flow demands during exercise, correction of endothelial dysfunction has become a goal of therapy. Endothelium-dependent coronary vasodilatation has been improved by a variety of interventions, including the use of agents such as angiotensin-converting-enzyme inhibitors,  $\beta$ -hydroxymethylglutaryl-coenzyme A reductase inhibitors, and antioxidants.<sup>3-6</sup>

Among the nonpharmacologic therapeutic options for patients with stable coronary artery disease, regular physical exercise is known to correct some risk factors for coronary artery disease and improve functional work capacity. In patients with symptomatic coronary artery disease, endurance exercise training has been shown to attenuate ST-segment depression during exercise<sup>7</sup> and decrease perfusion defects on thallium scanning,<sup>8</sup> indicating a possible increase in myocardial perfusion.

Advocates of exercise training for patients with coronary atherosclerosis have long faced the question of how exercise induces improvement in myocardial perfusion in the absence of any net regression of epicardial coronary stenoses.<sup>9</sup> Recruitment of collateral vessels during maximal exercise is one possible mechanism, but angiographic studies performed in patients at rest have failed to provide support for this hypothesis.<sup>10,11</sup>

The objective of this study was to determine whether aerobic exercise training has the potential to correct endothelial dysfunction and improve coronary flow reserve in patients with coronary artery disease.

### METHODS

#### Selection of Patients

Nineteen male patients (age,  $\leq 70$  years) with documented coronary artery disease were recruited. Patients were eligible for the

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study if they had a hemodynamically important coronary-artery stenosis that required nonsurgical revascularization (percutaneous transluminal coronary angioplasty) and a noncritical stenosis in another coronary vessel, which thus could be used for testing (the target vessel). To be suitable for testing, the target vessel had to have signs of endothelial dysfunction, defined as either constriction (a decrease of  $\geq 5$  percent in the mean luminal diameter) or no change (a decrease of  $< 5$  percent or no decrease in the mean luminal diameter) in response to acetylcholine. Patients also had to have a symptom-free exercise capacity of at least 50 W.

To minimize the effect of variables that could influence endothelial function, patients with any of the following conditions were excluded: diabetes, hypertension (a systolic blood pressure of  $> 160$  mm Hg or a diastolic blood pressure of  $> 90$  mm Hg), hypercholesterolemia (a low-density lipoprotein cholesterol level of  $\geq 165$  mg per deciliter [ $\geq 4.3$  mmol per liter]), cigarette smoking during the previous three months, ventricular tachyarrhythmias, chronic obstructive pulmonary disease, valvular heart disease, and a left ventricular ejection fraction of less than 40 percent. Patients who had undergone coronary-artery bypass graft surgery, had undergone a mechanical revascularization procedure during the previous three months, or had had myocardial infarction during the seven days before randomization were also excluded, as were patients with hematologic, renal, or hepatic dysfunction.

### Study Protocol

The protocol of this study was approved by the ethics committee of the University of Leipzig, and written informed consent was obtained from all patients before randomization. The same testing protocol was followed both for the initial study and for the follow-up study at four weeks.

Treatment with any cardiovascular medication was discontinued for at least 24 hours before the measurement of coronary endothelial function. At base line, patients were given 15,000 U of heparin after diagnostic coronary angiography or 24 hours after angioplasty in a vessel other than the target vessel, and an 8-French guiding catheter was used to cannulate the left or right coronary artery. A 2.5-French infusion catheter (Transit Infusion Catheter, Cordis, Miami, Fla.) was then advanced over a 0.014-in. (0.036-cm) guide wire into a nonbranching segment of the target vessel. This guide wire contained a 12-MHz, pulsed Doppler ultrasound velocimeter (FlowMAP, Cardiometrics, Endosonics, Rancho Cordova, Calif.). The tip of the guide wire was positioned 1 cm distal to the end of the infusion catheter, close to an anatomical landmark to facilitate its precise positioning at follow-up. The position of the tip of the guide wire was documented by cineangiography at the time contrast medium was injected. The maximal and mean peak blood-flow velocity measured by the Doppler velocimeter was continuously recorded throughout the test protocol and drug administration. For the assessment of coronary blood flow, the mean peak velocity was multiplied by the cross-sectional area of the vessel segment of interest to generate a value for the flow, expressed in milliliters per minute.

### Drug Administration

Saline (0.9 percent), acetylcholine (10 mg per milliliter; Dispersa, Germering, Germany), adenosine (3 mg per milliliter; Sanofi Winthrop, Munich, Germany), and nitroglycerin (1 mg per milliliter; Schwarz Pharma, Monheim, Germany) were administered through the infusion catheter. The agents were given in the following order: saline for three minutes (base line); acetylcholine in increasing doses (0.072, 0.72, and 7.2  $\mu\text{g}$  per minute); saline for three minutes (return to base line); adenosine (2.4 mg per minute); saline for five minutes (return to base line); and nitroglycerin (200  $\mu\text{g}$  as an intracoronary bolus). Three-minute intervals were allowed between drug infusions to permit all variables to return to base-line values. Saline, acetylcholine, and adenosine were infused with an infusion pump (Braun, Melsungen, Germany) set to a flow rate of 2 ml per minute.

### Quantitative Angiography

Serial coronary angiograms were obtained in the same projection at the end of each infusion, as follows. A nonionic contrast agent (Xenetrix, Guerbet, Sulzbach, Germany) was manually injected at low pressure through the guiding catheter. The artery of interest was centered and magnified, and then the image was digitized for subsequent computer analysis, as previously described.<sup>12</sup> The mean diameter of a 10-mm segment of interest was measured 2 to 3 mm distal to the tip of the Doppler guide wire before the infusion of acetylcholine and then after the infusion of each successive dose, after the infusion of adenosine, and after the administration of nitroglycerin. The response of the segment was calculated as the percent change in the mean diameter of the segment after the infusion of acetylcholine at each dose as compared with its initial diameter after saline infusion. The mean luminal diameter was determined with the use of an edge-detection algorithm (Medis, Leiden, the Netherlands). The contrast-filled distal catheter was used as the standard for calibration.

Maximal flow-dependent coronary vasodilatation was calculated by measuring changes in the target-vessel diameter proximal to the tip of the infusion catheter after the administration of adenosine. Coronary blood-flow reserve was calculated as the ratio of the mean peak coronary blood-flow velocity after the administration of adenosine to the coronary blood-flow velocity with the patient at rest.<sup>13</sup>

### Follow-up Studies

Two days after the invasive assessment of endothelial function, patients underwent symptom-limited spirometric testing during exercise for the determination of peak oxygen uptake. The patients exercised in the upright position on a calibrated, electronically braked bicycle ergometer. The work load was increased every three minutes in steps of 25 W, beginning at 50 W. The invasive assessment of endothelium-dependent vasodilatation and exercise testing were repeated after four weeks.

### Exercise-Training Program

After the initial study, patients were randomly assigned to either an exercise-training group or a physically inactive control group. Patients assigned to exercise training stayed in the hospital for the initial four weeks of the study period. They were expected to exercise, under close supervision, six times per day for 10 minutes (in addition to 5 minutes for warming up and 5 minutes for cooling down during each session); they exercised on a bicycle ergometer at 80 percent of the heart rate they had reached during peak oxygen uptake in the initial exercise test. The mean ( $\pm$ SE) heart rate reached during peak oxygen uptake in the initial test was  $134.4 \pm 3.8$  beats per minute, a value that was influenced by beta-adrenergic-receptor blockade in patients taking a beta-blocker (90 percent of the patients in this group). Thus, during this four-week period, patients trained at a mean heart rate of  $108.3 \pm 3.0$  beats per minute.

Patients assigned to the control group resumed treatment with their previous medications after the initial study, continued their sedentary lifestyle, and were supervised by their private physicians.

### Statistical Analysis

All data are expressed as means  $\pm$ SE. Both the absolute values and the percentage changes from base-line values were used in the statistical analyses; the two types of analysis yielded similar P values. Comparisons within each group and between the groups were performed with the use of two-way repeated-measures analysis of variance, followed by a post hoc Tukey test. Data were tested for normal distribution with the Kolmogorov-Smirnov test and for homogeneity of variances with Levene's test. The Mann-Whitney U test was used to compare the percentage changes (from the initial study to the follow-up assessment at four weeks) between the two treatment groups. A P value of less than 0.05 (by two-tailed testing) was considered to indicate statistical significance.

## RESULTS

## Base-Line Characteristics

Nineteen patients were randomly assigned to the exercise-training group (10 patients) or to the control group (9 patients). In the initial study, patients in the control group did not differ significantly from those in the exercise-training group (Table 1). Of the 19 target vessels selected for study, 14 (74 percent) were the left anterior descending coronary artery, 4 (21 percent) the circumflex coronary artery, and 1 (5 percent) the nondominant right coronary artery.

The two groups did not differ significantly with respect to medical treatment at base line. Patients were taking beta-blockers (90 percent of the patients in the exercise-training group and 78 percent of the patients in the control group), angiotensin-converting-enzyme inhibitors (60 percent and 44 percent, respectively), nitrates (30 percent and 56 percent), and calcium antagonists (0 percent and 11 percent). Their treatment did not change during the four-week period before enrollment or during the four-week follow-up period.

## Clinical Follow-up

One patient in the exercise-training group had a temporary third-degree atrioventricular conduction block during the initial infusion of adenosine. No adenosine was administered to this patient during the follow-up examination.

During exercise training, the body weight of patients in the exercise-training group remained essentially unchanged ( $83.4 \pm 4$  kg before training vs.  $82.5 \pm 4$  kg after training), as did metabolic variables that

might affect endothelial function, including the serum total cholesterol level ( $193 \pm 8$  mg per deciliter [ $5.0 \pm 0.2$  mmol per liter] before training vs.  $193 \pm 8$  mg per deciliter after training), the low-density lipoprotein cholesterol level ( $135 \pm 8$  mg per deciliter [ $3.5 \pm 0.2$  mmol per liter] vs.  $128 \pm 8$  mg per deciliter [ $3.3 \pm 0.2$  mmol per liter]), and the serum triglyceride level ( $115 \pm 18$  mg per deciliter [ $1.3 \pm 0.2$  mmol per liter] vs.  $106 \pm 9$  mg per deciliter [ $1.2 \pm 0.1$  mmol per liter]) (P not significant for any comparison).

After four weeks of exercise training, peak oxygen uptake during exercise increased by 12 percent (from  $24.0 \pm 1.5$  to  $26.8 \pm 1.0$  ml per kilogram of body weight per minute), whereas no significant change was observed in the control group ( $23.3 \pm 1.1$  vs.  $23.1 \pm 1.1$  ml per kilogram per minute,  $P < 0.05$  for the comparison between the groups).

## Response to Acetylcholine

In the initial study, patients in the exercise-training and control groups had similar responses to acetylcholine, expressed as the percentage change from base line in the luminal diameter after the infusion of increasing doses of acetylcholine. In the exercise-training group, the mean decreases in the luminal diameter after infusions of 0.072, 0.72, and 7.2  $\mu$ g of acetylcholine per minute were  $5.3 \pm 1.5$ ,  $11.0 \pm 2.4$ , and  $15.2 \pm 2.2$  percent, respectively; in the control group, they were  $3.2 \pm 1.3$ ,  $7.4 \pm 1.7$ , and  $10.9 \pm 2.1$  percent (P not significant).

After four weeks of exercise training, the mean vasoconstrictive responses to the intermediate dose of acetylcholine (0.72  $\mu$ g per minute) and the highest dose (7.2  $\mu$ g per minute) were significantly attenuated in comparison with the responses in the initial study. Coronary-artery constriction was reduced by 48 percent (from  $0.29 \pm 0.06$  to  $0.15 \pm 0.05$  mm) and 54 percent (from  $0.41 \pm 0.05$  to  $0.19 \pm 0.07$  mm) at the respective doses ( $P < 0.05$  for the comparison with the percentage change in the control group, at both doses) (Fig. 1 and Table 2).

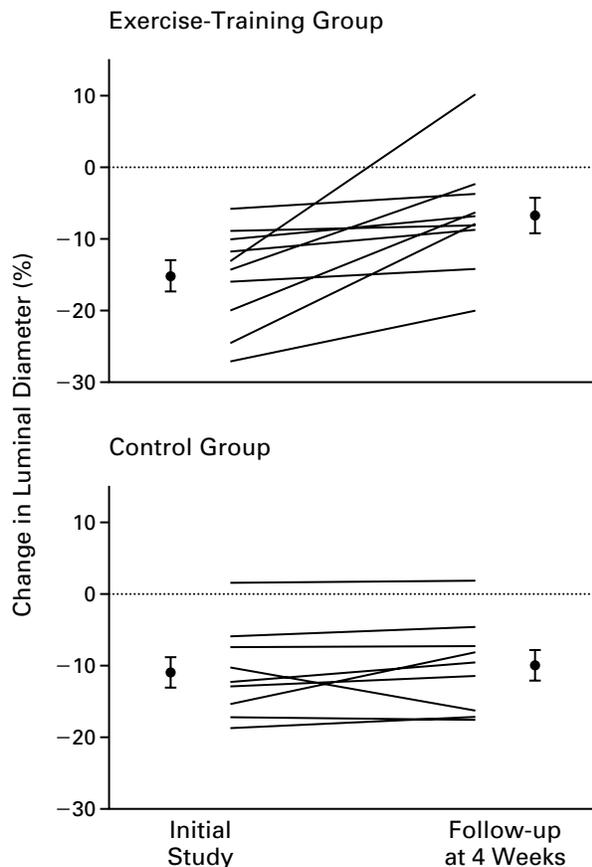
Exercise training led to significantly greater increases in coronary blood-flow velocity from base line. The increase was 96 percent (from  $4.6 \pm 2.8$  cm per second at the initial study to  $9.0 \pm 3.6$  cm per second at four weeks) with acetylcholine at a dose of 0.072  $\mu$ g per minute ( $P < 0.05$  for the comparison with the change in the control group), 73 percent (from  $11.7 \pm 4.4$  to  $20.2 \pm 3.5$  cm per second) at a dose of 0.72  $\mu$ g per minute ( $P < 0.01$  for the comparison with the change in the control group), and 73 percent (from  $21.9 \pm 4.2$  to  $37.8 \pm 3.6$  cm per second) at a dose of 7.2  $\mu$ g per minute ( $P < 0.01$  for the comparison between groups) (Table 3).

After four weeks of exercise training, the change in coronary blood flow in response to acetylcholine administration increased in a dose-dependent manner. At the highest dose of acetylcholine, the change

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS AT THE TIME OF THE INITIAL STUDY.\*

VARIABLE	EXERCISE- TRAINING GROUP (N=10)	CONTROL GROUP (N=9)	P VALUE
Age — yr	$60 \pm 2$	$61 \pm 1$	0.90
Left ventricular ejection fraction — %	$68 \pm 3$	$63 \pm 3$	0.26
History of myocardial infarction — no. of patients	2 (20)	3 (33)	0.51
No. of diseased vessels — no. of patients (%)			0.17
1	4 (40)	7 (78)	
2	6 (60)	2 (22)	
Stenosis of target vessel — % of diameter	$26.4 \pm 4.2$	$27.9 \pm 3.5$	0.93
Arterial blood pressure — mm Hg			
Systolic	$132 \pm 6$	$126 \pm 6$	0.77
Diastolic	$76 \pm 5$	$70 \pm 3$	0.59
Serum cholesterol — mmol/liter			
Total	$5.0 \pm 0.2$	$5.2 \pm 0.2$	0.56
Low-density lipoprotein	$3.5 \pm 0.2$	$3.4 \pm 0.2$	0.93

\*Plus-minus values are means  $\pm$  SE. To convert values for serum cholesterol to milligrams per deciliter, divide by 0.02586.



**Figure 1.** Individual Changes in Coronary-Vessel Luminal Diameter in Response to Acetylcholine at a Dose of 7.2  $\mu\text{g}$  per Minute at the Initial Study and after Four Weeks.

The mean percent change differed significantly between the groups at four weeks ( $P < 0.05$  for the comparison with the initial study). Negative values indicate decreases in diameter. Each line represents the change in an individual subject, and the solid circles and bars represent the group means  $\pm$  SE.

in mean coronary blood flow increased from  $27 \pm 11$  percent above base line at the initial study to  $110 \pm 24$  percent above base line at four weeks (from  $36 \pm 18$  to  $185 \pm 38$  ml per minute) ( $P < 0.01$  for the comparison between groups) (Fig. 2).

In the control group, the changes in vessel diameter and blood-flow velocity in response to acetylcholine infusion at four weeks were not significantly different from those in the initial study.

#### Endothelium-Independent Coronary Vasodilatation

The vasodilatory response of the epicardial arteries in response to the endothelium-independent vasodilator nitroglycerin remained essentially unchanged after four weeks of exercise training (an increase of  $0.27 \pm 0.03$  mm in luminal diameter before training vs. an increase of  $0.28 \pm 0.06$  mm after training;  $P$  not

**TABLE 2.** EFFECT OF EXERCISE TRAINING ON CORONARY-VESSEL DIAMETER.\*

DRUG AND DOSE	EXERCISE-TRAINING GROUP		CONTROL GROUP	
	INITIAL STUDY	FOLLOW-UP AT 4 WEEKS	INITIAL STUDY	FOLLOW-UP AT 4 WEEKS
	% change in diameter			
Acetylcholine				
0.072 $\mu\text{g}/\text{min}$	$-5.3 \pm 1.5$	$-3.7 \pm 1.7$	$-3.2 \pm 1.3$	$-2.9 \pm 0.9$
0.72 $\mu\text{g}/\text{min}$	$-11.0 \pm 2.4$	$-5.6 \pm 1.8 \dagger$	$-7.4 \pm 1.7$	$-6.7 \pm 1.5$
7.2 $\mu\text{g}/\text{min}$	$-15.2 \pm 2.2$	$-6.8 \pm 2.5 \dagger$	$-10.9 \pm 2.1$	$-10.0 \pm 2.2$
Adenosine	$10.2 \pm 2.4$	$14.0 \pm 3.3$	$10.7 \pm 3.2$	$9.7 \pm 2.2$
Nitroglycerin	$9.9 \pm 1.1$	$11.0 \pm 3.0$	$10.6 \pm 3.0$	$15.4 \pm 5.1$

\*Plus-minus values are means  $\pm$  SE. Changes are expressed as the percentage change in luminal diameter with drug administration, as compared with base-line conditions. Negative values indicate decreases.

$\dagger P < 0.05$  for the comparison with the change in the control group.

**TABLE 3.** EFFECT OF EXERCISE TRAINING ON MEAN PEAK CORONARY BLOOD-FLOW VELOCITY.\*

DRUG AND DOSE	EXERCISE-TRAINING GROUP		CONTROL GROUP	
	INITIAL STUDY	FOLLOW-UP AT 4 WEEKS	INITIAL STUDY	FOLLOW-UP AT 4 WEEKS
	% change in mean peak flow velocity			
Acetylcholine				
0.072 $\mu\text{g}/\text{min}$	$11.8 \pm 6.6$	$27.0 \pm 7.1$	$8.2 \pm 1.8$	$9.4 \pm 5.4$
0.72 $\mu\text{g}/\text{min}$	$36.4 \pm 11.1$	$73.0 \pm 19.0 \dagger$	$23.6 \pm 5.4$	$17.8 \pm 8.6$
7.2 $\mu\text{g}/\text{min}$	$78.1 \pm 15.5$	$141.6 \pm 27.7 \dagger$	$65.2 \pm 13.6$	$56.9 \pm 16.9$
Adenosine	$177.7 \pm 17.3$	$257.5 \pm 24.1 \dagger$	$241.2 \pm 26.3$	$228.7 \pm 21.7$
Nitroglycerin	$119.3 \pm 16.2$	$132.9 \pm 24.4$	$149.2 \pm 22.8$	$140.3 \pm 17.7$

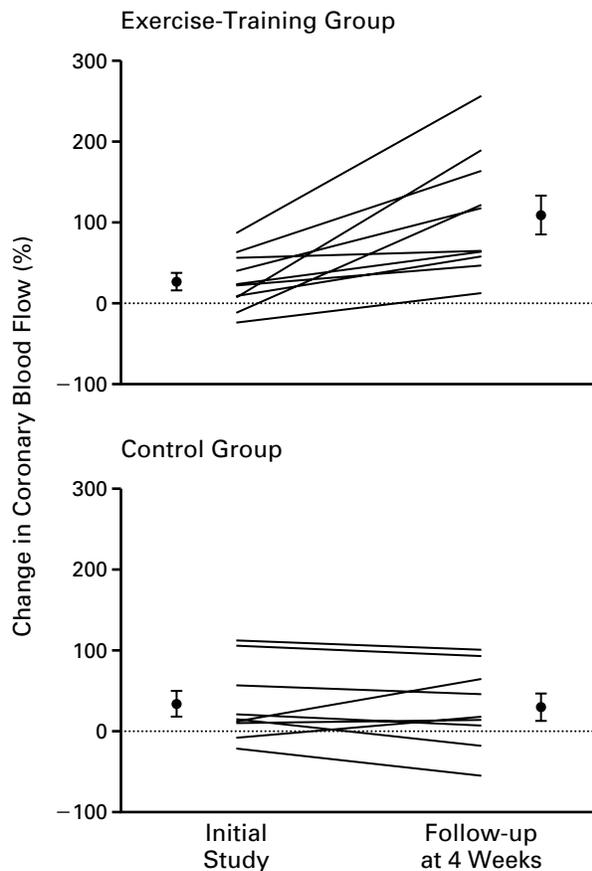
\*Plus-minus values are means  $\pm$  SE. Changes are expressed as the percentage change in velocity with drug administration, as compared with base-line conditions.

$\dagger P < 0.01$  for the comparison with the control group.

significant). The maximal increase in coronary blood flow caused by nitroglycerin was  $168 \pm 23$  percent at the initial study and  $188 \pm 33$  percent after four weeks of exercise training; the difference was not significant, and the effect of nitroglycerin in the control group was similar.

#### Coronary Blood-Flow Reserve and Flow-Dependent Dilatation

Coronary blood-flow reserve as assessed by adenosine infusion (the mean peak flow velocity after the administration of adenosine, divided by the velocity when the patient was at rest) improved significantly with exercise training (from  $2.8 \pm 0.2$  to  $3.6 \pm 0.2$ , a 29 percent change;  $P < 0.01$  for the comparison between groups). The adenosine-induced change in the diameter of the proximal target-vessel segment (ex-



**Figure 2.** Individual Changes in Coronary Blood Flow in Response to Acetylcholine at a Dose of  $7.2 \mu\text{g}$  per Minute at the Initial Study and after Four Weeks.

The mean percentage differed significantly between the groups at four weeks ( $P < 0.01$ ). Negative values indicate decreases in coronary blood flow. Each line represents the change in an individual subject, and the solid circles and bars represent the group means  $\pm$  SE.

posed to increased flow but not directly to adenosine) was measured in all patients, with the exception of one patient in the exercise-training group, in whom a temporary, adenosine-induced third-degree atrioventricular block developed during the initial study. Exercise training led to a significant increase in flow-dependent dilatation (from  $0.19 \pm 0.06$  to  $0.39 \pm 0.07$  mm, a 105 percent change;  $P < 0.01$  for the comparison between groups). In the control group, coronary blood-flow reserve and adenosine-induced changes in proximal-vessel diameter after four weeks did not differ significantly from the results at the initial study.

## DISCUSSION

We found that four weeks of vigorous exercise training improved coronary endothelial function in pa-

tients with asymptomatic coronary atherosclerosis. Coronary vasoconstriction in response to acetylcholine was significantly attenuated after exercise training, indicating that exercise had beneficial effects on the endothelium of epicardial conduit vessels. In agreement with this result was the finding that adenosine-induced flow-dependent vasodilatation after training was markedly improved.

In addition, we found that exercise training was associated with increases in agonist-mediated blood-flow velocity and coronary blood-flow reserve. These findings indicate that in the absence of clinically significant coronary-artery stenosis, the vasodilatory capacity of coronary resistance vessels was enhanced.

However, in this study, a four-week period of high-intensity endurance training improved the endothelial response to acetylcholine but did not restore it to normal levels, suggesting that the restoration of normal endothelial function may require a more extended exercise-training intervention. In studies of patients with symptomatic coronary artery disease, long-term exercise training was associated with a significant reduction in the incidence and severity of exercise-induced myocardial ischemia.<sup>7,9,14</sup> It is reasonable to suppose that in these patients myocardial perfusion was augmented after training.

Several mechanisms have been proposed to explain the enhanced myocardial perfusion in patients with coronary artery disease who undertake exercise training. They include regression of coronary artery disease, recruitment of coronary collateral vessels, and enhanced blood flow. As regards the first, most studies have failed to document a net regression of coronary lesions, even with the addition of lipid-lowering strategies to exercise-training interventions.<sup>14</sup> Moreover, a decrease in the incidence of myocardial ischemia was observed in patients with progression of stenotic lesions.<sup>9</sup> This unexpected result implies that improvement in myocardial perfusion may be achieved independently of changes in coronary lesions.

As regards the second, evidence from studies in animals suggests that long-term intensive exercise leads to an improvement in coronary collateralization.<sup>15,16</sup> However, angiographic studies performed at rest in patients with coronary artery disease did not substantiate this hypothesis.<sup>10</sup> Finally, blood viscosity can be reduced and blood flow can be improved by exercise training in healthy subjects and in patients with peripheral vascular disease.<sup>17</sup> However, in patients with coronary artery disease and impaired left ventricular function, exercise training did not have any significant effect on blood viscosity.<sup>18</sup> The reasons for the differences among these groups in their responses to exercise remain obscure.

None of the proposed mechanisms fully explain the beneficial effect of regular exercise on myocardial perfusion. However, this does not imply that these mechanisms are irrelevant to the observed improve-

ment in myocardial perfusion in the exercise-training groups. Rather, these mechanisms may have an effect at the level of another important structure regulating coronary perfusion, the vascular endothelium.

It is conceivable that improved endothelial function and coronary blood-flow reserve after exercise training reduce stress-induced myocardial ischemia despite increases in myocardial oxygen consumption. Our results suggest that it may be impaired endothelium-dependent coronary vasodilatation on which exercise has the most potent effect. This hypothesis is consistent with the results of interventional studies in patients with hypercholesterolemia. A marked decrease in the serum cholesterol level was associated with a correction of endothelial dysfunction,<sup>5</sup> improvement in myocardial perfusion,<sup>19</sup> and a decrease in the incidence of myocardial ischemia.<sup>6</sup> Because patients with the classic risk factors known to affect endothelial function (diabetes, hypertension, hypercholesterolemia, and smoking) were excluded from our study, the study groups do not reflect the typical population of patients with coronary artery disease.

Exercise training may correct endothelium-dependent vasodilatation of conduit coronary arteries by a variety of mechanisms. First, cell-culture experiments have demonstrated that shear stress augments the expression of nitric oxide synthase in endothelial cells. This finding is consistent with studies in dogs in which an increased expression of endothelial nitric oxide synthase was documented in coronary resistance vessels.<sup>20</sup> Second, shear stress induces up-regulation of the cytosolic copper-and-zinc-containing superoxide dismutase, a free-radical scavenger. The inactivation of nitric oxide by a vascular superoxide or other reactive oxygen species may thereby be attenuated.<sup>21</sup> Third, shear-stress-mediated suppression of angiotensin-converting enzyme may influence endothelium-dependent relaxation by affecting local concentrations of bradykinin, since angiotensin-converting enzyme is able to break down bradykinin into its inactive metabolites.<sup>22</sup>

In our assessment of nitroglycerin-induced, endothelium-independent coronary vasodilatation, we observed no differences between the exercise-training group and the control group. Short-term exercise training in patients with coronary atherosclerosis did not seem to alter the responsiveness of smooth-muscle cells of the coronary vasculature to the exogenous application of nitric oxide. Haskell and coworkers, however, demonstrated that the epicardial coronary arteries of highly trained, middle-aged endurance runners had a significantly greater dilating capacity in response to nitroglycerin than did those of healthy but inactive men.<sup>23</sup> It is conceivable that high-intensity endurance training over a long period may be necessary to increase the capacity of coronary vessels for endothelium-independent dilatation among patients with coronary atherosclerosis. It is also possi-

ble that in the present trial, the dose of nitroglycerin infused was sufficiently greater than the concentration of reactive oxygen species that small changes in vascular oxygen radicals had no detectable effect on nitroglycerin-induced vasodilatation.

Several mechanisms may influence coronary resistance vessels and the microcirculation after high-intensity exercise training. In studies in animals, it has been conclusively demonstrated that exercise training is associated with an increase in the total cross-sectional area of the vascular bed<sup>24</sup> and with enhanced sensitivity of coronary resistance vessels to adenosine<sup>25</sup> and other metabolic vasodilators.<sup>26</sup> None of these proposed mechanisms have yet been confirmed in humans, however.

In patients with coronary atherosclerosis, exercise training partially improves the endothelial function of large coronary conduit and resistance vessels. This finding provides a pathophysiologic framework for the elucidation of the positive effects of exercise on myocardial perfusion and emphasizes the therapeutic potential of endurance training for patients with stable coronary artery disease.

The catheters used in this study were provided by A.D. Krauth Cardiovascular (Hamburg, Germany).

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