Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 37, No. 7, 2001
ISSN 0735-1097/01/$20.00
PII S0735-1097(01)01236-0

Exercise Training Intervention After Coronary Angioplasty: The ETICA Trial

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OBJECTIVES The goal of this study was to determine the effects of exercise training (ET) on functional capacity and quality of life (QOL) in patients who received percutaneous transluminal coronary angioplasty (PTCA) or coronary stenting (CS), the effects on the restenosis rate and the outcome.

BACKGROUND It is unknown whether ET induces beneficial effects after coronary angioplasty.

METHODS We studied 118 consecutive patients with coronary artery disease (mean age 57 ± 10 years) who underwent PTCA or CS on one (69%) or two (31%) native epicardial coronary arteries. Patients were randomized into two matched groups. Group T (n = 59) was exercised three times a week for six months at 60% of peak $\dot{V}O_2$. Group C (n = 59) was the control group.

RESULTS Only trained patients had significant improvements in peak $\dot{V}O_2$ (26%, $p < 0.001$) and quality of life (26.8%, $p = 0.001$ vs. C). The angiographic restenosis rate was unaffected by ET (T: 29%; C: 33%, P = NS) and was not significantly different after PTCA or CS. However, residual diameter stenosis was lower in trained patients (−29.7%, $p = 0.045$). In patients with angiographic restenosis, thallium uptake improved only in group T (19%; $p < 0.001$). During the follow-up (33 ± 7 months) trained patients had a significantly lower event rate than controls (11.9 vs. 32.2%, RR: 0.71, 95% confidence interval [CI]: 0.60 to 0.91, $p = 0.008$) and a lower rate of hospital readmission (18.6 vs. 46%, RR: 0.69, 95% CI: 0.55 to 0.93, $p < 0.001$).

CONCLUSIONS Moderate ET improves functional capacity and QOL after PTCA or CS. During the follow-up, trained patients had fewer events and a lower hospital readmission rate than controls, despite an unchanged restenosis rate. (J Am Coll Cardiol 2001;37:1891–900) © 2001 by the American College of Cardiology

In the last 20 years, the introduction of coronary angioplasty (CA) has dramatically reduced the morbidity and mortality caused by coronary artery disease (CAD). However, because of restenosis, a repeated intervention is required in 25% to 40% of patients within 6 to 12 months (1). Almost half of the patients, after an initial encouraging improvement in functional capacity and quality of life (QOL) after the procedure, deal with recurrent chest pain that requires medical attention, reduces functional capacity and creates a status of psychological distress (2). Therefore, there is a need to develop strategies, not only to prevent restenosis but also to improve patients' functional status and perception of well-being.

Exercise training (ET) induces beneficial effects in patients with CAD (3,4). Several investigators have demonstrated not only specific changes in the muscular, cardiovascular and neurohumoral systems that lead to an improvement in functional capacity (5,6) but also a reduction in the ischemic response to a submaximal work rate after exercise conditioning (7). Moreover, mounting evidence suggests that ET determines regression or delays the progression of CAD and improves endothelial function (8,9). It is unclear, however, whether the beneficial effects of regular exercise observed in patients with native coronary artery stenoses can be applied to patients who underwent CA. In particular, it is not well defined whether ET can reduce the restenosis rate and improve the outcome.

The purpose of this study was to longitudinally assess the effects of ET of moderate intensity on functional capacity and QOL in a group of consecutive patients with CAD who underwent successful PTCA or coronary stenting (CS). We also evaluated whether these effects can translate into a reduced restenosis rate and a favorable outcome.

METHODS

We prospectively enrolled 130 consecutive patients (110 men, 20 women, mean age 57 ± 10 years) with CAD. Inclusion criteria were a successful procedure of CA in one or two native epicardial coronary arteries and ability to exercise. Exclusion criteria were previous CA procedures, cardiogenic shock, unsuccessful angioplasty (defined as a residual stenosis greater than 30% of the initial value), complex ventricular arrhythmias, uncontrolled hypertension and diabetes mellitus, creatinine ≥2.5 mg/dl, orthopedic or neurological limitations to exercise or unstable angina after the procedure and before the enrollment.

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Manuscript received August 14, 2000; revised manuscript received January 26, 2001, accepted February 12, 2001.

Abbreviations and Acronyms

AMI = acute myocardial infarction
BP = blood pressure
CA = coronary angioplasty
CABG = coronary artery bypass surgery
CAD = coronary artery disease
CI = confidence interval
CS = coronary stenting
ET = exercise training
LV = left ventricle, left ventricular
MET = metabolic equivalent
PTCA = percutaneous transluminal coronary angioplasty
QOL = quality of life
RR = relative risk
$\dot{V}O_2$ = oxygen uptake

Protocol. The protocol was approved by the local ethical committee. All patients signed an informed consent. Patients were randomized into two matched groups. Group T underwent ET, while group C was recommended to be sedentary and not to exercise regularly. Of the initial 130 patients enrolled, eight patients in the T group and four patients in the C group were excluded for various reasons. Three developed orthopedic limitations; five were hospitalized for noncardiac reasons; and four had personal problems. As shown in Table 1, groups were well balanced for pathophysiological and clinical variables. Primary angioplasty, defined as angioplasty without thrombolytic therapy, was performed 148 ± 63 min after the onset of an acute myocardial infarction (AMI) in 23 patients (11 in group T, 12 in group C). Medications were given according to internationally accepted protocols (10). They were similarly distributed in the two groups and remained unchanged throughout the study. Lipid-lowering drugs were not allowed during the study, because we aimed specifically to assess the effects of ET on lipid profile (see Study limitations section). The coronary risk profile was also similar in the two groups (Table 1). An improvement in the coronary risk profile was considered a ≥9% reduction in serum total cholesterol level, alone or in combination with smoking cessation and ≥5% reduction in blood pressure (BP) (2 SD of the average reduction after ET in our laboratory). After 25 ± 7 days from the successful procedure, all patients underwent an exercise test with gas exchange analysis, an echocardiographic study and a myocardial scintigraphy. The three tests were repeated at six months. Coronary angiography was performed immediately after the procedure in all patients and was repeated in 104 patients (n = 52 in each group) at six months. All studies were performed by experienced operators and evaluated by two independent observers blinded to treatment arm and to each other's interpretation. A third observer was asked to resolve differences when agreement was not achieved. A consensus decision was obtained in all cases.

ET. Exercise sessions were performed at the hospital gym and were supervised by a cardiologist. The program lasted six months and consisted of three exercise sessions per week at an intensity of 60% of peak oxygen uptake ($\dot{V}O_2$). After a 15-min phase of stretching and calisthenics, patients pedaled on an electronically braked cycle ergometer at the target work rate for 30 min. This working phase was preceded by a 5-min loadless warm-up and followed by 3 min of unloaded cool-down pedaling. Control patients were recommended to perform basic daily mild physical activities but to avoid any physical training. A list of acceptable physical activities was provided, together with a diary to report daily activities.

Cardiopulmonary exercise test. After a familiarization test, a symptom-limited cardiopulmonary exercise test was performed on an electronically braked cycle ergometer using a ramp protocol, as previously described (7). The exercise test was stopped when one or more of the following criteria were present: predicted heart rate, fatigue, dyspnea, excessive systemic BP increase (≥230/130 mm Hg), ≥1 mm ST depression in at least two adjacent leads or angina. The anaerobic threshold was measured by the V-slope method (11). Peak $\dot{V}O_2$ was considered the average $\dot{V}O_2$ during the last 15 s of exercise.

Echocardiography. On study entry and at six months, all patients underwent an echocardiographic study, following the recommendations of the American Society of Echocardiography (12). We used an ultrasound system with a two-dimensional mechanical sector scanner (2.5 MHz, ESAOTE, Italy). The reproducibility of echocardiographic measurements at Lancisi has been published recently (13).

Myocardial scintigraphy. A planar (Apex, Elscint, Israel) myocardial scintigraphy was performed using a stress-redistribution-reinjection protocol, as previously described (7).

DATA ANALYSIS. The left ventricle (LV) was divided into 15 segments, and thallium uptake was graded on a five-point scale from 0 (normal) to 4 (absent) (qualitative analysis) and by circumferential count profiles analysis (quantitative analysis) (7). A thallium activity score index was defined as the sum of the thallium score of each myocardial segment divided by the number of segments analyzed.

Thallium images of the follow-up studies were compared side by side with the corresponding baseline scans. Improvement in thallium uptake from baseline was defined as an increase in thallium uptake on follow-up scans by at least 1 grade in any of the three acquisition imaging series.

Coronary angiography. Coronary angiography was performed by Judkins' technique. Two studies were performed—the first immediately after CA and the second after a mean of 178 ± 22 days from the beginning of the protocol. A stenosis was considered hemodynamically significant if a ≥50% reduction in luminal diameter was measured. A successful CA, performed by a femoral route according to the technique of Gruentzig et al. (14), was defined as <30% residual diameter stenosis on the coronary

Table 1. Population Study, Lesion and Procedural Characteristics

Variable	Exercise (n = 59)	Control (n = 59)	p Value
Clinical			
Men/Women	49/10	50/9	0.96
Age, yr	53 ± 11	59 ± 10	0.20
Myocardial infarction, n (%)	30 (51)	28 (47)	0.81
Ejection fraction, %	52 ± 16	50 ± 14	0.47
Hypercholesterolemia, n (%)	36 (61)	32 (54)	0.56
Diabetes, n (%)	10 (17)	12 (20)	0.86
Cigarette smokers, n (%)	40 (68)	37 (62)	0.62
Systemic hypertension, n (%)	25 (42)	28 (47)	0.72
Obesity, n (%)	9 (16)	6 (10)	0.49
Angiographic			
Diseased vessels (%)			
1	38	42	0.80
2	30	28	0.97
3	32	30	0.97
IRA, (%)	58	52	0.64
Lesion type, (%)			
A	50	54	0.80
B_1	20	16	0.74
B_2	10	12	0.96
C	20	18	0.97
Coronary lesion score	1.95 ± 0.9	1.89 ± 0.8	0.70
Coronary collateral score	0.9 ± 0.8	1.1 ± 0.9	0.21
Angioplasty			
Coronary artery, (%)			
LAD	62	64	0.97
Cx	20	20	0.82
RC	18	16	0.97
PTCA/stent, n	19/40	18/41	0.77/0.94
Single/multiple, n (%)	40/19 (67.8/32.2)	41/18 (69/30.6)	0.90/0.77
Number of stents	1.3 ± 0.8	1.4 ± 0.9	0.53
Type of stent, (%)			
Palmaz-Schatz	18	20	0.97
NIR	45	45	0.85
AVE	25	25	0.83
Other	12	10	0.96
Stented segment length, mm	12.4 ± 9	13.5 ± 8.5	0.50
Residual DS, (%)			
≤10%	65	70	0.70
10–30%	35	30	0.70
Balloon-to-vessel ratio	1.05 ± 0.13	1.06 ± 0.15	0.67
Maximal balloon pressure, atm	11.7 ± 2.6	12 ± 2.8	0.55

Hypercholesterolemia was defined as serum total cholesterol >200 mg/dL; hypertension was defined as systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg. Medications (number of patients) = exercise group: aspirin (59), ticlopidine (34), calcium antagonists (59), nitrates (55); control group; aspirin (59), ticlopidine (36), calcium antagonists (59), nitrates (58). p values by chi-square.

AVE = stent with a wire zig-zag segment design (Arterial Vascular Engineering); Cx = circumflex artery; DS = diameter stenosis; IRA = infarct-related artery; LAD = left anterior descending artery; NIR = stent with a continuous multicellular uniform design (SCIMED); PTCA = percutaneous transluminal coronary angioplasty; RC = right coronary artery.

angiogram immediately after the procedure, associated with a Thrombolysis in Myocardial Infarction flow grade 2. All procedures (PTCA or stent) were performed in a significant stenosis of the proximal two-thirds of one or two major epicardial coronary arteries. The choice of balloon or stent type, pressure and duration of inflation were left at the discretion of the operator. In all patients, nitrates, aspirin and calcium channel blockers were given before the procedure, and heparin was started during the procedure. Four patients in the treatment arm and three patients in the control arm received the glycoprotein IIb/IIIa inhibitor abciximab intravenously (0.25 mg/kg bolus followed by 0.125 μg/kg per min) immediately after the procedure. A primary angioplasty was performed in the infarct-related artery of patients admitted to the hospital because of chest pain started ≤3 h earlier and associated with ST-segment elevation in at least two adjacent leads.

DATA ANALYSIS. Quantitative analysis was performed in each angiogram with a computer-assisted edge detection system (Digital Cardiac Imaging, Philips, The Netherlands). At follow-up angiography, changes in coronary

stenoses from baseline study were scored as 0 when a <20% change or any change was detected, +1 when >20% change was observed and −1 when a negative difference of >20% was evident. Restenosis was defined by a diameter stenosis >50% at follow-up coronary angiography in any location subjected to balloon inflation or stent placement during the angioplasty procedure. Progression/regression of CAD was defined as an increase/decrease of more than 20% in a pre-existing diameter stenosis. New stenosis was defined as >20% diameter stenosis in one or more coronary arteries in any other segments not subjected to angioplasty. We used a cutoff value of 20% because it reflects 2 SD of the difference between repeated measurements in our research and in other laboratories (8).

Two experienced interventional cardiologists independently interpreted the studies in a blinded manner. Disagreement between the two observers was resolved by consensus.

QOL. Quality of life was assessed with two questionnaires (Duke Activity Status Index and MOS short-form General Health Survey) (15,16). Both questionnaires were administered just before the enrollment and at 6 and 12 months.

Follow-up and outcome measures. Follow-up started the day after the completion of the protocol and lasted 33 ± 7 months. All patients were visited at the hospital during the run-in phase and at three and six months. During each visit, a 12-lead electrocardiogram was performed, and BP was measured. Follow-up ended with an adverse event. Measures of outcome were prospectively defined as mortality from all causes and cardiovascular morbidity (AMI, new CA, or coronary artery bypass surgery [CABG]). Both the exercise and the control groups were subjected to the same scrutiny and management regimen, apart from the exercise component.

Statistical analysis. All analyses were performed on an intention-to-treat basis, and probability values were two-sided. Chi-square statistics and unpaired *t* tests were performed to assess differences between groups at baseline. Changes in the exercise group were compared with changes in the control group by the Mann-Whitney *U* test. Intraobserver and interobserver agreement for any echocardiographic, scintigraphic or angiographic initial and follow-up images were assessed by kappa statistics and expressed as Kendall's coefficient of concordance. We also divided the changes in peak $\dot{V}O_2$ by terciles using cutoff points in change from baseline to follow-up of <1.75 mL/kg/min and 3.5 mL/kg/min of $\dot{V}O_2$ (corresponding to 1 metabolic equivalent [MET]) and considered functional capacity for each patient as being unchanged (<1.75 mL/kg/min), moderately improved (1.75 to 3.5 mL/kg/min) or largely improved (>3.5 mL/kg/min). We then compared the changes in QOL scores, both overall and for each subscale, with each category of change in functional capacity. To verify whether the improvement in events could be simply collinear with improved risk profile, we used a multiple stepwise regression with events, thallium uptake and coronary risk factors as independent variables and exercise training as dependent variable. We also performed a logistic regression analysis with CAD progression as dependent variable and exercise as independent variable, after adjustment for changes in measured risk factors. Cox proportional hierarchical hazards model was used to assess the relative risk (RR) and 95% confidence intervals (CI) in order to compare outcomes between groups. Kaplan-Meier survival analysis was also performed, and cardiac event rates as well as hospital readmission rate in trained and untrained patients were compared by log-rank test. Data are mean ± SD. Statistical significance was accepted for $p < 0.05$.

RESULTS

All patients completed the training regimen. There were no significant adverse cardiovascular events during the exercise sessions. Compliance with the training program, defined as percentage of sessions attended, was 94% (range, 84% to 100%).

Hemodynamic and metabolic changes. As shown in Table 2 at six months, improvements in hemodynamic and ventilatory variables were evident only in trained patients. The majority of trained patients had ≥1 MET increase in functional capacity (highest tercile: n = 31; middle tercile: n = 18; lowest tercile: n = 8). By contrast, no control patients were in the highest tercile; four were in the middle and 10 were in the lowest tercile. All the remaining 45 control patients had a final peak $\dot{V}O_2$ lower than the initial.

Coronary risk profile. At six months, compared with controls, trained patients had significant improvements as reflected by the coronary risk profile (Table 2). The combination of smoking cessation with BP-lowering was predictive of peak $\dot{V}O_2$ change after ET (β −0.76; p = 0.02).

Echocardiography. As shown in Table 3, on initial evaluation there were no significant differences in LV diameters and volumes between the two groups. At six months, however, trained patients had a significant reduction in end-systolic volume and a significant increase in ejection fraction and systolic wall thickening score index compared with controls. All these improvements were more marked in trained patients who underwent primary CA.

Myocardial scintigraphy. As shown in Table 3, on study entry there was no difference in thallium activity on stress or delayed images between the two groups. However, at six months, compared with control patients, trained patients had a lower increase in the number of segments with abnormal thallium uptake on stress images and a greater increase in the number of completely reversible myocardial defects on delayed images. These changes were paralleled by an improvement in thallium uptake score index, evident only in the training group. At six months, a thallium score ≥1.65 identified patients with a lower rate of cardiac events during the follow-up. Five of 55 patients with a score ≤1.65 and 21 of 54 patients with a score >1.65 had cardiac events ($p < 0.001$). The improvement in thallium uptake was

Table 2. Metabolic and Clinical Variables on Study Entry and After Six Months in Training and Control Groups

	Exercise Group		Control Group		
	Study Entry	6 Months	Study Entry	6 Months	p*
Cardiopulmonary Exercise Test					
Heart rate, rest, beats/min	70 ± 12	65.4 ± 15	68 ± 18	66 ± 21	0.38
Heart rate, peak, beats/min	135 ± 28	141 ± 27	138 ± 25	139 ± 29	0.32
Systolic blood pressure, rest, mm Hg	128 ± 29	122 ± 31	125 ± 19	131 ± 21	0.01
Systolic blood pressure, peak, mm Hg	181 ± 21	196 ± 28	188 ± 23	180 ± 25	< 0.001
Peak oxygen uptake, mL/Kg/min	18.6 ± 4.6	23.7 ± 7.9	20.5 ± 4.4	19.4 ± 4.2	< 0.001
Peak oxygen uptake, mL/min	1,526 ± 449	1,910 ± 481	1,492 ± 436	1,498 ± 468	< 0.001
Peak carbon dioxide output, mL/min	1,770 ± 463	2,255 ± 441	1,715 ± 398	1,723 ± 421	< 0.001
Ventilatory threshold, mL/Kg/min	10.3 ± 4.2	13.1 ± 4.5	10.8 ± 3.8	9.9 ± 4.4	< 0.001
Ventilation, L/min	58.5 ± 17	74.2 ± 20	62 ± 21	58.4 ± 24	< 0.001
O_2 $pulse_{75\ watts}$	8.7 ± 3.2	10.4 ± 2.8	7.9 ± 3.5	7.4 ± 3.7	< 0.001
Respiratory exchange ratio	1.16 ± 0.4	1.18 ± 0.4	1.15 ± 0.5	1.15 ± 0.6	0.82
Coronary Risk Factors					
Cigarette smokers, n (%)	40 (68)	5 (8.5)	37 (62)	16 (27)	0.005
Total cholesterol, mg/dL	235 ± 33	212 ± 31	225 ± 41	255 ± 45	< 0.001
LDL-cholesterol, mg/dL	148 ± 41	131 ± 42	138 ± 38	148 ± 41	< 0.001
HDL-cholesterol, mg/dL	34 ± 19	39.2 ± 16	36 ± 25	32 ± 28	0.02
Triglycerides, mg/dL	178 ± 55	155 ± 41	181 ± 62	189 ± 58	0.02
Body mass index	2.43 ± 0.8	2.22 ± 0.8	2.39 ± 0.9	2.4 ± 0.8	0.14

*p values refer to change in value between treated and control patients by Mann-Whitney rank sum test.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

correlated with an improvement in the coronary risk profile ($r = 0.71$, $p < 0.001$).

Coronary angiography. Follow-up coronary angiography was performed in 104 patients (n = 52 in each group) (Table 4).

ANGIOGRAPHIC RESTENOSIS. Angiographic restenosis was detected in 15 of 52 trained patients (29%) and 17 of 52 controls (33%; $p = 0.81$). In both groups, the restenosis rate was similar after PTCA or stent (exercise group: PTCA 19%, stent 10%; control group: PTCA 25%, stent 8%; $p = 0.95$ and 0.85, respectively) and after primary angioplasty (group T: 24%; group C: 36%; $p = 0.41$ and 0.26, respectively). However, as shown in Table 4, diameter stenosis was significantly higher in untrained, compared with trained, patients ($p = 0.045$) without differences between PTCA or stent, and, within the training group, it was lower in patients who received PTCA ($p = 0.005$ vs. stent). In both groups, angiographic restenosis was more frequent in patients with ejection fraction <45%, multiple risk factors and in the presence of angulated vessels, multi-

Table 3. Echocardiographic and Scintigraphic Studies at Baseline and Six Months in Trained and Control Patients

	Exercise Group		Control Group	
	Study Entry	6 Months	Study Entry	6 Months
Echocardiography				
Left ventricular end-diastolic diameter (cm)	5.41 ± 0.5	5.52 ± 0.4	5.36 ± 0.5	5.44 ± 0.6
Left ventricular end-systolic diameter (cm)	3.78 ± 0.4	3.71 ± 0.6	3.92 ± 0.6	3.96 ± 0.7
Fractional shortening (%)	29.8 ± 0.5	32.7 ± 0.5	26.9 ± 0.6	27.2 ± 0.7
Left ventricular end-diastolic volume (mL)	89.1 ± 19	93.2 ± 18	94.2 ± 21	97.3 ± 20
Left ventricular end-systolic volume (mL)	42.4 ± 15	40.8 ± 16*	46.7 ± 12	48.8 ± 14
Ejection fraction (%)	52.3 ± 16	57.3 ± 15†	50.2 ± 14	49.3 ± 15
Systolic wall thickening score index	1.43 ± 0.4	1.35 ± 0.4‡	1.51 ± 0.5	1.66 ± 0.7
Myocardial Scintigraphy				
^{201}Tl uptake				
All segments (n of pts)	885 (59)	855 (57)	885 (59)	780 (52)
Normal uptake, % of total segments	67	62§	64	48
Abnormal uptake, % of total segments	33	38§	36	52
Completely reversible, n of segments (n of pts)	41 (22)	80 (32)‖	58 (25)	66 (28)
Partially reversible, n of segments (n of pts)	146 (40)	128 (34)	126 (42)	130 (43)
Reversible after reinjection, n of segments (n of pts)	17 (11)	20 (11)	26 (13)	47 (18)
^{201}Tl activity score index	1.88 ± 0.99	1.52 ± 1.01‖	1.92 ± 1.2	1.96 ± 1.2

*p = 0.009 vs. C; †p = 0.02 vs. C; ‡p = 0.01; §p = 0.03; ‖p = 0.001 by Mann-Whitney rank sum test, change in value between treated and controls.
n of pts = number of patients.

Table 4. Results of Follow-up Angiography

	Exercise Group			Control Group		
	Study 1	Study 2	Study 3	Study 1	Study 2	Study 3
All procedures						
Mean luminal diameter (mm)	0.44 ± 11	3.09 ± 0.4	1.93 ± 1.4	0.39 ± 0.45	3.2 ± 0.4	1.58 ± 0.78
Diameter stenosis (%)	77.3 ± 18	11 ± 13	41 ± 28*	80.2 ± 15	9 ± 16	53.2 ± 27
PTCA						
Mean luminal diameter (mm)	0.39 ± 10	3.05 ± 0.5	1.87 ± 1.1	0.42 ± 0.5	3.01 ± 0.5	1.38 ± 0.9
Diameter stenosis (%)	81 ± 16	12 ± 10	34 ± 20†	87 ± 17	10 ± 9	49 ± 21
Stent						
Mean luminal diameter (mm)	0.42 ± 0.4	3.12 ± 0.6	2.1 ± 1.4	0.41 ± 0.6	3.14 ± 0.5	1.8 ± 1.1
Diameter stenosis (%)	79 ± 12	8 ± 7	45 ± 19‡§	82 ± 14	9 ± 10	58 ± 21

Study 1: initial evaluation; study 2: immediately after coronary angioplasty; study 3: follow-up. *p = 0.045 vs. C; †p < 0.001 vs. C; ‡p = 0.004 vs. C; §p = 0.005 vs. PTCA within group T.
PTCA = percutaneous transluminal coronary angioplasty.

ple and eccentric stenoses before coronary angioplasty and small vessel size (<2.8 mm) ($p < 0.05$ for all). Patients who received more than one consecutive stent had a higher restenosis rate than patients with one stent (65% vs. 35%, $p = 0.02$). Exercise training did not modify this trend. Multivariate analysis demonstrated that changes in measured risk factors were not independent predictors of restenosis.

CORONARY LESIONS. The progression of coronary artery disease was significantly lower in trained patients than it was in control patients at six months. New lesions in major epicardial arteries were found in four patients in group T (7.6%) and in 13 patients in group C (25%; $p = 0.038$). New narrowings were more frequent in the angioplasty than in the nonangioplasty artery (35% vs. 15%, $p < 0.001$), in particular in segments closer to a stented region. No change in preexisting coronary stenoses was detected in 45 trained patients and 39 controls, while regression was observed in three trained patients and none of the controls. A correlation was found between changes in coronary lesions and changes in the coronary risk profile ($r = -0.67$, $p = 0.001$). However, exercise, after controlling for changes in measured risk factors, was the only independent predictor of CAD progression (β −1.49, $p = 0.0006$).

CORONARY COLLATERALS. Coronary collateral score was not significantly different at follow-up angiography in both groups (group T: 1.4 ± 0.6; group C: 1.1 ± 0.7) and was not correlated with the restenosis rate as well as CAD progression. A weak correlation was found between residual diameter stenosis and coronary collateral score only in trained patients ($r = 0.46$; $p < 0.05$).

QOL. Quality of life, assessed by DASI and MOS questionnaires, significantly improved after exercise training. As shown in Table 5, both DASI and MOS total scores improved significantly after six months ($p = 0.001$ vs. controls for both) and remained significantly higher in trained patients than it did in controls at 12 months. The improvement in scores was significantly higher in trained patients with >1 MET increase in functional capacity at six months ($p < 0.01$).

Stepwise multiple regression analysis with changes in peak $\dot{V}O_2$ as dependent variable selected MOS Health Perception ($r = -0.76$, $p = 0.001$) and Mental Health ($r = -0.52$, $p = 0.014$) as the best correlated variables.

Cardiac events. Of the 118 patients included in the analysis, 26 (22%) had cardiac events, nine during the training period and 17 during the follow-up. All events were nonfatal. As shown in Table 6, cardiac events were more frequent in the control group (19 vs. 7, $p = 0.008$). During the initial six months after CA, two patients in the training group and seven patients in the control group had cardiac events. The two patients in the training group were with-

Table 5. Quality of Life as Assessed by the Duke Activity Status Index (DASI) and Medical Outcomes Study (MOS) Questionnaires in Training and Control Groups

	Exercise Group			Control Group		
	Test 1	Test 2	Test 3	Test 1	Test 2	Test 3
DASI	41 ± 11	52 ± 10*	53 ± 12*	40 ± 9	45 ± 11	35 ± 13
MOS:						
Physical functioning	50 ± 21	78 ± 19*	82 ± 18*	48 ± 18	55 ± 20	54 ± 20
Role functioning	66 ± 12	75 ± 13†	76 ± 9†	62 ± 15	65 ± 14	58 ± 14
Social functioning	62 ± 9	66 ± 10	68 ± 11	60 ± 11	69 ± 12	68 ± 12
Mental health	45 ± 12	65 ± 12†	70 ± 14*	45 ± 14	48 ± 15	45 ± 15
Health perception	58 ± 15	68 ± 14*	70 ± 14*	56 ± 18	50 ± 19	50 ± 18
Pain	10 ± 5	4 ± 9*	4 ± 9*	12 ± 8	22 ± 10	32 ± 12
MOS total‡	271 ± 74	348 ± 77*	362 ± 75*	264 ± 84	265 ± 90	243 ± 91

Test 1: study entry; test 2: 6 months; test 3: 12 months. *p = 0.001 vs. control; †p = 0.01 vs. control by multiple analysis of variance; ‡the score of the subcategory "Pain" has been subtracted from MOS total score.

Table 6. Cardiac Events According to Study Group and Cause

	Group T (n = 59)	Group C (n = 59)	Absolute Difference*	Relative Risk (95% CI)†	p value
	n (%)	n (%)	%		
Cardiac deaths	0	0	0	—	—
Coronary angioplasty	4 (6.8)	11 (18.6)	−10.2	0.84 (0.76–1.05)	0.19
Acute myocardial infarction	1 (1.7)	3 (5.1)	−3.4	1.05 (0.68–1.59)	0.31
Coronary artery bypass surgery	2 (3.4)	5 (8.5)	−5.1	0.99 (0.76–1.46)	0.26
All‡	7 (11.9)	19 (32.2)	−20.3	0.71 (0.60–0.91)	0.008

*Difference between the percentage of events in the trained group and the percentage of events in the control group; †relative risk and CI were estimated from the Cox proportional-hazards model; ‡all patients who underwent a new coronary angioplasty or bypass surgery were hospitalized for unstable angina (13), low-threshold effort angina (8) or low-threshold myocardial ischemia during exercise stress testing (5).
CI = confidence interval.

drawn from the exercise program because of unstable angina. Both patients had coronary restenosis. One of them underwent a new angioplastic procedure at the site of previous PTCA, while the other had CABG (three-vessel disease). Of the seven untrained patients, five underwent CS, three at the site of a previous PTCA and two on a new significant stenosis; two patients had an AMI with no evidence of angiographic restenosis. During the follow-up period, of the trained patients, two had a new procedure (i.e., CS); two underwent CABG, and one had an AMI. Among untrained patients, six underwent a new PTCA; five underwent CABG, and one had an AMI. In the survival model (Fig. 1), trained patients had a significantly lower event rate than control patients (log-rank 8.15, $p < 0.005$). Multivariate analysis demonstrated that the improvement in events was not collinear with changes in the coronary risk profile and thallium uptake, and the only independent predictor of events was exercise training ($p = 0.008$). Trained patients also had a lower rate of hospital readmission than control patients group (18.6% vs. 46%, RR: 0.69, 95% CI: 0.55 to 0.93, $p < 0.001$) and a reduced need for further revascularization (10% vs. 27%, RR: 0.78, 95% CI: 0.66 to 0.89, $p = 0.03$). Causes of hospital readmission were angina pectoris (6 patients from group T, 17 patients from group C), atypical chest pain (three patients from group C) and low threshold myocardial ischemia during exercise testing (five patients from group T, one patient from group C). As shown in Figure 2, there was a significant difference

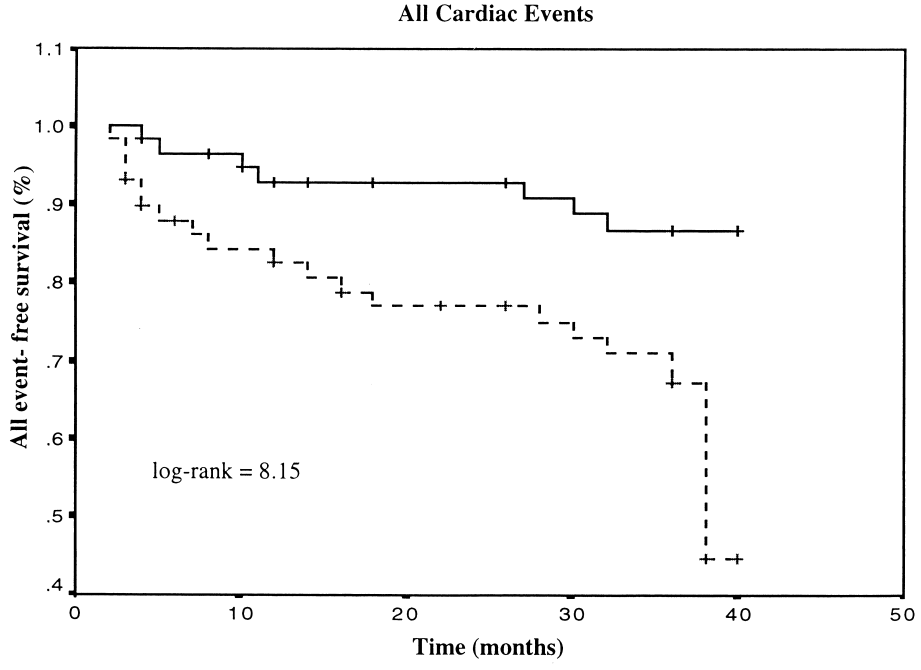
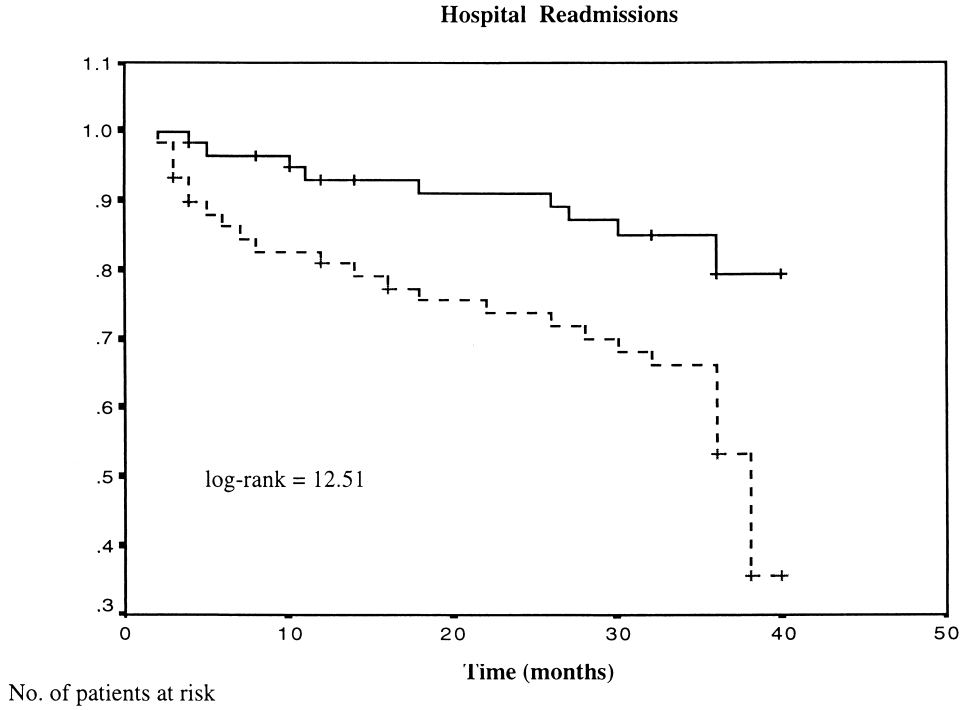


Figure 1. Kaplan-Meier curves of all event-free survival in trained patients **(solid line)** and untrained controls **(broken line)** during follow-up. + = censored cases.



No. of patients at risk

Trained	59	54	52	49	48
Untrained	59	49	42	38	32

Figure 2. Kaplan-Meier curves of hospital readmissions in trained patients **(solid line)** and untrained controls **(broken line)** during follow-up. + = censored cases.

between hospital readmission curves when separated by exercise training (log rank: 12.51, $p < 0.001$).

DISCUSSION

The results of this longitudinal, randomized and controlled study demonstrate that moderate ET improves functional capacity and QOL after PTCA or stent. These beneficial effects seem to translate into a favorable outcome.

Functional capacity and QOL. Exercise training significantly improves functional capacity in patients with ischemic heart disease (17). However, information about the effects of ET after PTCA or stent is lacking. A previous report demonstrated a 15% increase in functional capacity after ET in patients who underwent balloon-PTCA in a single stenosis of a native coronary artery (18). A more recent study showed that a multifactorial lifestyle program combining stress management, diet, exercise and smoking habit changes improves exercise capacity after PTCA (19). In both studies, peak $\dot{V}O_2$ was not measured, and no information about the outcome was provided.

In trained patients, we found a 26% increase in peak $\dot{V}O_2$, which correlated with an improvement in QOL ($r = 0.78$; $p < 0.001$). These benefits were similar after PTCA or stent and were associated with improvements in the coronary risk profile. In particular, the combination of smoking cessation with BP-lowering was an independent predictor of peak $\dot{V}O_2$ change ($p = 0.02$) (20). The improvement in peak $\dot{V}O_2$ at six months was not correlated with the type of procedure (PTCA or stent), type of stent, number of dilated vessels, collateral score or the primary approach. In contrast with these results, the ACME study demonstrated a greater functional capacity in patients who received PTCA than those seen in controls (25.9% vs. 6.8% from baseline) (21).

The results of this study demonstrate that the improvement in QOL after ET is mainly related to changes in functional capacity and the coronary risk profile, while progression of CAD or restenosis do not play a significant role. In fact, there was no correlation between either functional capacity or QOL and restenosis rate and coronary lesion severity, respectively. Among patients with restenosis, trained patients had a more significant improvement in QOL than those who were untrained. These improvements were maintained at 12 months, that is, six months after the end of the exercise program. It is conceivable that training-induced improvements in LV systolic function, combined with metabolic as well as peripheral adaptations, may allow a sustained improved perception of well being through a more active lifestyle.

Restenosis and CAD progression. The results of this investigation suggest that ET can attenuate neointimal growth after PTCA or stent, but this effect is not sufficient to reduce the restenosis rate. The restenosis rate was higher in patients who received more than one consecutive stent. Stent implantation imposes significant alterations in physical factors, such as shear stress and tensile forces, that cause

injury of intimal as well as medial smooth muscle cells and extracellular matrix. As a result, stented segments have a decreased capacity to dilate in response to physical or chemical stimuli, and intimal thickening generally occurs. A lower residual diameter stenosis despite unchanged restenosis has also been described after a single-vessel balloon CA in patients who underwent moderate ET (18). It is possible that ET, by increasing hemodynamic shear stress, improves nitric-oxide mediated dilation of coronary segments with intact endothelium and reduces neointimal hyperplasia and remodeling of the stented segment (22).

CAD PROGRESSION. Trained patients had a lower progression of CAD than untrained controls at follow-up angiography (7.6% vs. 25%, $p = 0.038$). A similar effect has been described with a combined regimen of antianginal medications, exercise and diet (8). In contrast with this study, we obtained an overall improvement in the coronary risk profile only with ET, without any other specific intervention on the lifestyle. We found that, by controlling for changes in risk factors, exercise was an independent predictor of CAD progression ($p = 0.0006$). It is possible that exercise, by improving the endothelium-dependent dilation of coronary arteries and reducing the oxidative stress, may attenuate the progression of preexisting coronary artery stenoses and may prevent new atherosclerotic lesions (23).

ANGIOGRAPHY VERSUS SCINTIGRAPHY. The sensitivity of scintigraphy to detect restenosis was lower in trained patients than it was in untrained patients (53% vs. 70%). The two most likely explanations may be the higher progression of CAD in control patients and coronary vessel adaptations in trained patients. Both effects can lead to underestimation of myocardial defects by scintigraphy.

Outcome. As shown in Table 6, trained patients had less events than controls. The rate of new interventions was significantly higher in untrained patients with restenosis over the same follow-up period (12 of 29; $p < 0.01$). Trained patients who had restenosis were more asymptomatic than untrained controls during the follow-up. At six months, an improved myocardial perfusion predicted a better outcome despite angiographic restenosis.

The results of this study suggest that ET exerts a major role in this improvement. In fact, ET was an independent predictor of events and was not collinear with changes in perfusion or the coronary risk profile. It is possible that ET, by improving endothelial dysfunction, can reduce the recurrence of myocardial ischemia. In the presence of a significant coronary stenosis, intermittent bouts of submaximal constant work rate exercise can improve flow-mediated dilation of coronary arteries (9) and can also raise adenosine concentration in the interstitium, leading to vasodilation and new vessels growth (24).

Both mechanisms can explain the improvement in myocardial perfusion in trained patients, even if they had evidence of angiographic restenosis.

Study limitations. Lipid-lowering drugs were not allowed during the study. This can be considered unethical on the basis of the results of recent trials that demonstrated a reduced mortality in patients receiving statins (25). However, at the time of enrollment (1993), such information was not available. Moreover, it is possible that, since some of the effects of chronic exercise are mediated by the observed decrease in cholesterol, this effect might diminish if statins had been used.

A structural bias was that patients were not blinded to the treatment arm. Another possible bias was that control patients were not checked three times per week as was the treated group. On the other hand, treated patients had frequent interactions with the medical environment, and this could have amplified benefits from exercise. Finally, not all cardiac risk factors were measured, and those not measured might be lower in treated patients and might be associated with some benefits.

Conclusions. These findings suggest that long-term ET of moderate intensity is safe and improves functional capacity and QOL after both PTCA and stent. These benefits are associated with a lower rate of hospital readmissions and a lower need for further revascularization procedures. The improvement in events was correlated with ET and was not collinear with changes in thallium uptake and risk factors. Even in the presence of angiographic restenosis, ET can improve myocardial perfusion of the territory distal to stenosis, suggesting anatomical or functional adaptations of coronary vessels. Moreover, the development of new epicardial coronary stenoses is reduced in trained patients, in part by an improved coronary risk factor profile induced by physical conditioning.

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REFERENCES

1. Popma JJ, Califf RM, Topol EJ. Clinical trials of restenosis after coronary angioplasty. Circulation 1991;84:1426–6.
2. Feuerstein GZ. Restenosis: basic research and clinical perspective. In: Feuerstein GZ, editor. Coronary Restenosis. From Genetics to Therapeutics. New York, NY: Marcel Dekker Inc., 1997:1–4.
3. Thompson PD. The benefits and risks of exercise training in patients with chronic coronary artery disease. J Am Med Assoc 1988;259: 1537–40.
4. O'Connor GT, Buring JE, Yusuf S, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. Circulation 1989;80:234–44.
5. Clausen JP. Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and patients with coronary artery disease. Prog Cardiovasc Dis 1976;18:459–95.
6. Ferguson RJ, Taylor AW, Cote P, et al. Skeletal muscle and cardiac changes with training in patients with angina pectoris. Am J Physiol 1982;243:H830–6.
7. Belardinelli R, Georgiou D, Ginzton L, et al. Effects of moderate exercise training on thallium uptake and contractile response to low-dose dobutamine of dysfunctional myocardium in patients with ischemic cardiomyopathy. Circulation 1998;97:553–61.
8. Schuler G, Hambrecht R, Schlierf G, et al. Regular physical exercise

and low-fat diet: effects on progression of coronary artery disease. Circulation 1992;86:1–11.
9. 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.
10. Ryan TJ, Bauman WB, Kennedy JW, et al. Guidelines for percutaneous transluminal coronary angioplasty: a report of the ACC/AHA Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedure. J Am Coll Cardiol 1993;22:2033–52.
11. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 1986;60:2020–7.
12. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989;2:358–67.
13. Belardinelli R, Georgiou D, Purcaro A. Low-dose dobutamine echocardiography predicts improvement in functional capacity after exercise training in patients with ischemic cardiomyopathy: prognostic implication. J Am Coll Cardiol 1998;31:1027–34.
14. Gruentzig AR, Senning A, Siegenthaler WE. Nonoperative dilation of coronary artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979;301:61–8.
15. Hlatky MA, Boineau RE, Higginbotham MB, et al. A brief self-administered questionnaire to determine functional capacity (The Duke Activity Status Index). Am J Cardiol 1989;64:651–4.
16. Stewart AL, Hays RD, Ware JE, Jr. The MOS short-form general health survey. Reliability and validity in a patient population. Med Care 1988;26:724–35.
17. Oldridge NB, Guyatt GH, Fisher ME, Rimm AA. Cardiac rehabilitation after myocardial infarction: combined experience of randomized clinical trials. JAMA 1988;260:945–50.
18. Kubo H, Yano K, Hirai H, et al. Preventive effect of exercise training on recurrent stenosis after percutaneous transluminal coronary angioplasty (PTCA). Jpn Circ J 1992;56:413–21.
19. Hofman-Bang C, Lisspers J, Nordlander R, et al. Two-year results of a controlled study of residential rehabilitation for patients treated with percutaneous transluminal coronary angioplasty. A randomized study of a multifactorial program. Eur Heart J 1999;20:1465–74.
20. Kokkinos PF, Papademetriou V. Exercise and hypertension. Coron Artery Dis 2000;11:99–102.
21. Strauss WE, Fortin T, Hartigan P, Folland ED, Parisi AF, and the Veterans Affairs Study of Angioplasty Compared to Medical Therapy Investigators. A comparison of quality of life scores in patients with angina pectoris after angioplasty compared with after medical therapy. Outcomes of a randomized clinical trial. Circulation 1995;92:1710–9.
22. Kingwell BA. Nitric-oxide mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. FASEB J 2000:14:1685–96.
23. Leaf DA, Kleinman MT, Hamilton M, Deitrick RW. The exercise-induced oxidative stress paradox: the effects of physical exercise training. Am J Med Sci 1999;317:295–300.
24. Teuscher E, Weidlich V. Adenosine nucleotides, adenosine and adenine as angiogenesis factors. Biomed Biochem Acta 1985;44:493–5.
25. The Long-term Interventions with Pravastatin in Ischemic Disease (LIPID) Study Investigators. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.