

Clinical Investigation

Regular Physical Exercise and Low-Fat Diet Effects on Progression of Coronary Artery Disease

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Background. Significant regression of coronary and femoral atherosclerotic lesions has been documented by angiographic studies using aggressive lipid-lowering treatment. This study tested the applicability and effects of intensive physical exercise and low-fat diet on coronary morphology and myocardial perfusion in nonselected patients with stable angina pectoris.

Methods and Results. Patients were recruited after routine coronary angiography for stable angina pectoris; they were randomized to an intervention group ($n=56$) and a control group on "usual care" ($n=57$). Treatment comprised intensive physical exercise in group training sessions (minimum, 2 hr/wk), daily home exercise periods (20 min/d), and low-fat, low-cholesterol diet (American Heart Association recommendation, phase 3). No lipid-lowering agents were prescribed. After 12 months of participation, repeat coronary angiography was performed; relative and minimal diameter reductions of coronary lesions were measured by digital image processing. Change in myocardial perfusion was assessed by ^{201}Tl scintigraphy. In patients participating in the intervention group, body weight decreased by 5% ($p<0.001$), total cholesterol by 10% ($p<0.001$), and triglycerides by 24% ($p<0.001$); high density lipoproteins increased by 3% ($p=\text{NS}$). Physical work capacity improved by 23% ($p<0.0001$), and myocardial oxygen consumption, as estimated from maximal rate-pressure product, by 10% ($p<0.05$). Stress-induced myocardial ischemia decreased concurrently, indicating improvement of myocardial perfusion. Based on minimal lesion diameter, progression of coronary lesions was noted in nine patients (23%), no change in 18 patients (45%), and regression in 13 patients (32%). In the control group, metabolic and hemodynamic variables remained essentially unchanged, whereas progression of coronary lesions was noted in 25 patients (48%), no change in 18 patients (35%), and regression in nine patients (17%). These changes were significantly different from the intervention group ($p<0.05$).

Conclusions. In patients participating in regular physical exercise and low-fat diet, coronary artery disease progresses at a slower pace compared with a control group on usual care. (*Circulation* 1992;86:1-11)

KEY WORDS • coronary artery disease • exercise • diet

Previously published studies have shown that normalization of elevated abnormal lipoprotein levels retards progression of coronary or femoral atherosclerotic lesions; even regression of plaques may be induced in some patients.¹⁻⁶ These beneficial effects of lipid modification are associated with fewer clinical events and decreased mortality from coronary artery disease.⁶ By eliminating foods rich in saturated fats and cholesterol, correcting overweight, and exercising on a regular basis, satisfactory results can be achieved with respect to serum lipoprotein levels, provided patients can be motivated to dedicate their time and effort toward this goal.^{8,9} Therefore, the success of this form of therapy depends largely on the patient's determination and self-discipline to achieve certain goals with respect

to dietary changes and regular physical exercise. In hand-picked individuals endowed with exceptional motivation and determination, impressive changes are feasible⁹; in nonselected, average patients with coronary artery disease, effects of lifestyle intervention are modest.¹⁰ Nevertheless, after testing the feasibility of low-fat diet and regular physical exercise as a therapeutic regimen in a pilot study,⁷ this study was initiated to assess its effect on myocardial perfusion and the progression of coronary atherosclerosis.

Methods

Patient Selection and Assignment

Patients participating in this study were recruited after routine coronary angiography for angina pectoris. Inclusion criteria were male gender, stable symptoms, willingness to participate in the study for at least 12 months, coronary artery stenoses well documented by angiography, and permanent residence within 25 km of the training facilities at Heidelberg. Exclusion criteria were unstable angina pectoris, left main coronary artery stenosis >25% luminal diameter reduction, severely

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depressed left ventricular function (ejection fraction <35%), significant valvular heart disease, insulin-dependent diabetes mellitus, primary hypercholesterolemia (type II hyperlipoproteinemia, low density lipoprotein [LDL] >210 mg/dl), and occupational, orthopedic, and other conditions precluding regular participation in exercise sessions. All patients satisfying these conditions were offered the opportunity to participate; no one was rejected on the basis of "probable noncompliance."

After an introductory session during which patients were familiarized with the aims of the study, randomization process, and alternative therapeutic approaches, their written consent was obtained. Sealed envelopes were used to randomize patients between intervention and control groups.

The investigational protocol was approved by the ethical committee for human studies at the University of Heidelberg.

Cardiac Catheterization

Cardiac catheterization was performed by the femoral approach; left ventriculography in two orthogonal projections was followed by coronary angiography according to the Judkins technique. A minimum of six standard projections was obtained and supplemented by additional angulations to accomplish optimal visualization of all stenotic segments in several projections. During follow-up angiography at 12 months, identical projections were reproduced according to the protocol followed initially. Vasoactive drugs (nitroglycerin, calcium channel blockers) were stopped 24 hours before catheterization, and none were used during the procedure.

Digital Image Processing

Evaluation of coronary angiograms was performed by two technicians blinded to the sequence of films and the patient's identity or group assignment. Films were viewed in pairs using two 35-mm cineangiographic projectors (Vanguard Instruments Inc., Melville, N.Y.). Each segment of the coronary tree was examined carefully for changes in luminal diameter. After identification of stenoses, corresponding projections were lined up near end diastole; both regions of interest containing the stenotic segment were magnified $\times 2.5$ by optical zoom. Images were read by a television camera, and, after digitization, transferred to the image-processing system (KONTRON MIPRON), where they were stored in a 512×512 matrix. As all images were obtained in the 6-in. angiographic mode, pincushion distortion was minimal¹¹ and correction was not essential. Coronary vessel boundaries were identified by an automated edge-detection algorithm. The procedure for contour detection requires the operator to indicate several points located in the center of the magnified arterial segment. A definite centerline is calculated automatically, and digital data are sampled along straight lines perpendicular to the centerline. The vessel boundary is determined on the basis of the weighted sums of first and second derivative functions.¹² Minimal stenosis diameter (D_{\min}) is measured and compared with the adjacent normal reference diameter (D_r). Percentage diameter reduction is calculated as

$$\%D = \frac{D_r - D_{\min}}{D_r}$$

No attempt was made to calculate the longitudinal dimension of lesions or atherosclerotic mass, because these variables have demonstrated considerable variability.^{11,13} Because of the limited resolution of digital image processing, lesions located in side branches <1 mm in diameter were not analyzed.

To assess the interindividual variability of relative diameter reduction determination, 25 stenoses were analyzed three times on different days by three technicians. The standard deviation between repeated measurements of percentage diameter reduction was 4.4%. Consequently, only changes between sequential measurements exceeding 10% (2 SD) were considered as relevant. Stenoses with <10% change in diameter reduction were classified as unchanged (grade ± 0). A positive difference >10% between baseline and end was graded as progression (grade +1), and a negative difference >10% was graded as regression (grade -1). Any lesion necessitating intervention by percutaneous transluminal coronary angioplasty or coronary artery bypass surgery was given the grade +3.

Absolute minimal stenosis diameter was obtained by using the distal portion of the coronary catheter as a reference source. Variability of this method was assessed by measuring 30 coronary segments entirely free of atherosclerotic lesions at baseline and at 12 months. Mean absolute diameters differed by 1% (3.03 versus 2.99 mm); variability of individual measurements from baseline to 12 months was ± 0.09 mm. Therefore, changes exceeding ± 0.18 mm (2 SD) were graded as progression or regression, respectively. Changes in minimal stenosis diameter correlated well with changes of relative diameter reduction ($r=0.80$, $p<0.001$). If classification of patients was based on changes of minimal stenosis diameter instead of relative diameter reduction, the incidence of regression, progression, or no change was comparable (Table 8).

Progression from subtotal occlusion to total occlusion (99% to >100%) and recanalization of previously occluded coronary arteries were not classified as progression or regression, respectively, as mechanisms not related to the atherosclerotic process may be operative in these cases.¹⁴

Differences between both groups were evaluated on a per-patient basis (Table 8) and on a per-lesion basis (Table 9). In patients with multiple stenoses, the fate of each individual lesion probably cannot be considered statistically independent; therefore, each patient must be treated as a statistical unit. Moreover, in rare instances, progression and regression may occur side-by-side in one particular patient. Consequently, a single variable was calculated for each patient by adding the grades assigned to individual stenoses on the basis of percentage of diameter reduction or minimal diameter. Cases with a positive sum of grades (>0) were classified as progression, with a negative result (<0) as regression, whereas ± 0 was defined as no change.

Exercise Testing and ²⁰¹Tl Scintigraphy

β -Blockers and antianginal medications were discontinued 48 hours before the test. After an overnight

fasting period, symptom-limited ECG stress testing was performed on a treadmill using a modified Balke-Ware protocol.¹⁵ ECG tracings and blood pressure readings were obtained every minute. Exercise was terminated when patients experienced progressive anginal chest pain, physical exhaustion, or when 3-mm horizontal ST segment depression was reached. Maximal rate-pressure product (RPP) was calculated from maximal, simultaneously recorded heart rate and systolic blood pressure at the end point of exercise. This variable has been shown to correlate reliably with myocardial oxygen consumption ($\dot{M}V\text{O}_2$) over a wide range of exercise levels.^{16,17}

One minute before terminating the exercise test, 2 mCi ^{201}Tl was injected intravenously and exercise continued for another minute at the same or slightly reduced exercise level. Imaging was started immediately after termination of exercise with the use of a mobile gamma camera equipped with a seven-pin-hole collimator.^{18–20} Resting images were acquired after a resting period of 4 hours in the identical projection.

^{201}Tl scintigrams were analyzed by a technician blinded to the patient's identity. Left ventricular cross sections perpendicular to the long axis were reconstructed from the raw data. In these cross sections, the ischemic area was identified and expressed in degrees of left ventricular circumference. Stress-induced, reversible ischemia was calculated as the difference between early and redistribution images. This method was validated by comparing perfusion defects to histopathological findings in patients who died in the course of acute myocardial infarction.^{21,22}

Metabolic Variables

After an overnight fasting period, body weights were obtained and blood was drawn for measurements of serum lipids and lipoproteins (total cholesterol, LDL cholesterol, high density lipoprotein cholesterol [HDL], as well as triglycerides).^{7,23} Specimens were obtained at baseline, 3 weeks, and at 3, 6, 9, and 12 months. For data processing, all values obtained after initiation of therapy were averaged and compared with baseline.

Assessment of Dietary Compliance

Initially and at all follow-up visits, a detailed 24-hour dietary protocol was obtained. A computer program was used to calculate consumption of total energy, fat, carbohydrates, and cholesterol.²⁴ These results were correlated to objective measurements such as body weight, serum cholesterol, and triglyceride levels.

Blood Rheology

Blood was taken from the antecubital vein without tourniquet application using EDTA as anticoagulant. Plasma viscosity was determined by capillary viscometry using the Coulter-Harkness viscometer.²⁵ Erythrocyte aggregation was analyzed photometrically at an adjusted hematocrit of $45 \pm 1\%$, using a previously described aggregometer (Myrenne GmbH).²⁶ The rate constant of erythrocyte aggregate formation in stasis was determined by the increase in photovoltage during the first 8 seconds after mixing. The rate constant of erythrocyte aggregate formation was multiplied by plasma viscosity to correct for the damping of aggregate formation by plasma viscosity.²⁷

Psychological Assessment

Psychological testing and interviews were done on entry into the study and after 12 months of therapy. Patients' "health locus-of-control" (i.e., the tendency to attribute responsibility for one's own health and illness to oneself [internal orientation], to other people [personal-external orientation], or to chance factors [chance-external orientation]), as well as their degree of depression were assessed by means of self-report questionnaires.^{28,29} Patients who met the inclusion criteria to the study but decided not to participate were also asked to answer the initial set of questionnaires.

Intervention Program

Patients assigned to the intervention group stayed on a metabolic ward during the initial 3 weeks of the program, during which they were instructed how to lower the fat content of their regular diet.⁷ The guidelines they received were based on the American Heart Association recommendation, phase 3³⁰; it called for a low-fat, low-cholesterol diet (protein, 15%; carbohydrates, 65%; fat, <20% of energy; cholesterol, <200 mg; polyunsaturated-to-saturated fatty acids ratio, >1).

Patients were asked to exercise daily at home on a cycle ergometer for a minimum of 30 minutes close to their target heart rates, which were determined as 75% of the maximal heart rate during symptom-limited exercise. During this time, patients were on their regular antianginal medication, including β -blocking agents. In addition, they were expected to participate in at least two group training sessions of 60 minutes each week. Compliance for attending group exercise sessions was 68% (range, 39–92%). Assessment of compliance rates during home exercise was based on a log book kept by the patients; although evaluation of these log books yielded comparable results, it was less reliable for obvious reasons. Aspirin and antianginal medications, including nitrates, β -blockers, and calcium channel blockers were prescribed as indicated; lipid-lowering drugs were not part of the regimen.

Informative sessions were conducted at regular intervals five times a year for patients and their spouses to discuss dietary, psychosocial, and exercise-related problems. In addition, patients were offered opportunities to discuss personal questions and problems after each training session.

Control Group

Patients assigned to the control group spent 1 week on the metabolic ward, where they received identical instructions about the necessity of regular physical exercise and how to lower fat consumption. They were served a low-fat diet corresponding to the American Heart Association recommendations, phase 1,³⁰ and they were encouraged to participate in local coronary exercise groups. Adherence to these guidelines, however, was left to their own initiative, and "usual care" was rendered by their private physicians. They were asked not to take lipid-lowering medications.

Statistics

For statistical evaluation, nonparametric tests (Mann-Whitney *U* test, Wilcoxon signed rank test, Fisher's exact test) were used.³¹ Changes in psycholog-

TABLE 1. Patient Characteristics

	Intervention	Control
No. of randomized patients	56	57
Age (years)	52.8±5.8	54.2±7.7
Gensini score	28.8±16	27.6±19
Previous AMI (No.) (%)	31 (60)	40 (70)
LVEF (%)	57±9	55±8
Body mass index (kg/m ²)	26.7±2.5	26.4±2.2
Cholesterol (mmol/l)	6.05±1.00	6.09±1.03
HDL (mmol/l)	0.92±0.24	0.91±0.18
LDL (mmol/l)	4.24±0.69	4.25±0.85
Triglycerides (mmol/l)	1.97±0.81	2.16±1.24
Resting heart rate (l/min)	74±11	76±12
Resting systolic blood pressure (mm Hg)	128±19	128±21
Maximal heart rate (l/min)	142±17	151±20
Maximal systolic blood pressure (mm Hg)	188±24	190±27
Physical work capacity (W)	159±53	163±47
Maximal oxygen uptake (l/min)	1.8±0.4	1.9±0.5
Maximal rate-pressure product (l*10 ³)	26.9±5	28.6±6
²⁰¹ Tl perfusion defect	44±44°	42±37°

AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; HDL, high density lipoproteins; LDL, low density lipoproteins.

No significant difference between groups was detected for any variable (Mann-Whitney rank sum test, χ^2 analysis).

ical variables, as well as influence of metabolic variables and exercise compliance on change in coronary morphology, were examined by ANOVA. To examine sequential metabolic data for statistical significance, all measurements obtained after initiation of therapy (i.e., 3 weeks and 3, 6, 9, and 12 months) were averaged and compared with baseline using the Wilcoxon signed rank test; comparisons between groups were performed by ANOVA. Correlation coefficients were calculated by Pearson product-moment correlations.

Results

Patient Population

A total of 113 patients met the inclusion criteria and were recruited for the study; 56 patients were randomized to the intervention program and 57 to the control group (Table 1). Their mean age was 53.5 years (range, 35–68 years); severity of coronary artery disease (Gensini score)³³ and left ventricular performance was comparable in both groups; 66% of patients had sustained an acute myocardial infarction previously.

Dropouts and Clinical Events

Intervention group. Before initiation of therapy, five patients withdrew their consent for various nonmedical reasons, and one patient was scheduled for coronary artery bypass surgery by his private physician (Table 2). During the study period, there were four dropouts, and three patients were excluded from further participation because life-threatening arrhythmias (nonsustained ventricular tachycardia) were detected by Holter monitoring during the first training session. These patients underwent electrophysiological testing and were started on appropriate antiarrhythmic treatment; they have remained free of symptoms since then. There were three cardiac arrests: One patient greatly exceeded his training heart rate during group exercise by more than 30%, as documented by Holter monitoring, and experienced ventricular tachycardia; he was resuscitated by direct current countershock. The second patient died at home shortly after completing his daily cycle exercise. The third patient was found in the street with no vital signs; he was resuscitated but died later because of extensive brain damage. Balloon angioplasty was performed in two patients for unstable angina pectoris. Therefore, at 12 months, complete angiographic data were available in 40 patients.

Control group. One patient withdrew his consent before initiation of therapy. There were three dropouts, and one patient died of cancer. One patient experienced cardiac arrest in the course of an acute myocardial infarction but was successfully resuscitated; he later

TABLE 2. Clinical Events

Patient	Details of event	Cardiac status at baseline
Intervention		
9	Unstable angina; PTCA RCA at 12 months	3-Vessel disease; LVEF, 45%
10	Unstable angina; PTCA LAD at 12 months	1-Vessel disease; LVEF, 57%
40	Unwitnessed cardiac arrest at home; resuscitation; extensive brain damage; died 5 months later	3-Vessel disease; LVEF, 63%; AMI 6 months ago
42	Cardiac arrest after exercise at home; unsuccessful resuscitation	3-Vessel disease; LVEF, 35%; AMI 2 years ago
104	Cardiac arrest during group training session; resuscitation	2-Vessel disease; LVEF, 59%; AMI 1 year ago
Control		
11	Unstable angina; PTCA RCA at 12 months	3-Vessel disease; LVEF, 63%
21	Acute myocardial infarction; cardiac arrest; resuscitation; coronary bypass surgery	2-Vessel disease; LVEF, 33%; AMI 2 years ago
72	Acute myocardial infarction; PTCA LCx at 9 months	2-Vessel disease; LVEF, 49%; Lateral MI 1 year ago
86	Acute myocardial infarction; PTCA RCA at 9 months	1-Vessel disease; LVEF, 46%; AMI 1 year ago

PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex artery; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction (%).

TABLE 3. Number and Percentage of Patients on Medication

	Baseline (No.) (%)	12 Months (No.) (%)	Change (No.) (%)
Intervention (n=40)			
Nitrates	29 (73)	28 (70)	-1 (-3)
Calcium blockers	22 (55)	18 (45)	-4 (-10)
β -Receptor blockers	31 (78)	30 (75)	-1 (-3)
Aspirin	39 (98)	39 (98)	± 0 (± 0)
Control (n=52)			
Nitrates	36 (69)	37 (71)	+1 (+2)
Calcium blockers	31 (60)	28 (54)	-3 (-6)
β -Receptor blockers	38 (73)	40 (77)	+2 (+4)
Aspirin	50 (96)	50 (96)	± 0 (± 0)

underwent bypass surgery. Balloon angioplasty was performed in one patient for unstable angina pectoris and in two because of evolving myocardial infarction. At 12 months, angiographic data were available in 52 patients.

Medical Treatment

Intervention group. Initially, 78% of all patients were on β -blocking agents, 55% on calcium channel blockers, and 73% on nitrates (Table 3). At 12 months, the corresponding percentages were 75%, 45%, and 70%. No patient was on lipid-lowering drugs.

Control group. Initially, 73% of all patients were on β -blocking agents, 60% on calcium channel blockers, and 69% on nitrates. At 12 months, the corresponding percentages were 77%, 54%, and 71%. Lipid-lowering drugs were not prescribed to any patient.

Smoking Status

At baseline, six patients (11%) in the intervention group smoked (average, 8.1 cigarettes per day; range, 4–20); at 12 months, four patients (7%) continued to smoke 13.7 cigarettes per day (range, 5–20). In the control group, six patients (11%) smoked at baseline (average, 10.3 cigarettes per day; range, 1–25), at 12 months, seven patients (12%) smoked an average of 10.7 cigarettes per day (range, 5–25).

Dietary Changes According to 24-Hour Protocol

According to the 24-hour dietary protocols, patients in the intervention group made considerable changes in their dietary schedule: Total energy consumption decreased by 27% ($p < 0.001$), total fat consumption by 53% ($p < 0.001$), and cholesterol consumption by 62%

($p < 0.001$) (Table 4). Carbohydrate consumption remained unchanged, raising the contribution to total energy uptake from $38 \pm 10\%$ to $49 \pm 9\%$ ($p < 0.0001$).

Changes recorded in the control group were roughly half in magnitude compared with the intervention group: Total energy consumption decreased by 19% ($p < 0.001$), total fat consumption by 25% ($p < 0.001$), and total cholesterol uptake by 35% ($p < 0.001$), whereas carbohydrate consumption remained essentially unchanged (-5%), raising the contribution to total energy uptake from $40 \pm 8\%$ to $45 \pm 11\%$ ($p < 0.01$).

Metabolic Variables

Initially, body mass index (body weight, 26.4 ± 2.3 kg/m² [80.2 ± 8.5 kg]) and serum lipoproteins were only marginally elevated (total cholesterol, 6.07 ± 1.01 mmol/l [234 ± 40 mg/dl]) (Table 5, Figure 1). In the intervention group, body weight decreased by 5% ($p < 0.001$), total cholesterol by 10% ($p < 0.001$), LDL by 8% ($p < 0.002$), and triglycerides by 24% ($p < 0.001$); HDL increased by 3% ($p = \text{NS}$). In the control group, body weight and lipoprotein levels remained unchanged with the exception of triglycerides, which decreased by 17% ($p < 0.02$). Change in body weight was significantly correlated to change in cholesterol level ($r = 0.38$, $p < 0.001$), as previously described.³²

Compliance for attending group exercise sessions was significantly correlated with average total cholesterol levels during therapy ($r = -0.51$, $p < 0.001$), average LDL levels ($r = 0.49$, $p < 0.05$), and average triglyceride levels ($r = -0.51$, $p < 0.001$). No significant correlation was detected between physical fitness variables and lipoprotein levels.

When results obtained from the 24-hour dietary protocols were related to body weight and lipoprotein levels, no significant correlation was detected for any variable: Δ total energy uptake/ Δ body weight ($r = -0.02$), Δ cholesterol consumption/ Δ serum cholesterol ($r = 0.11$), Δ fat consumption/ Δ serum triglycerides ($r = 0.06$) ($\Delta =$ difference baseline versus 12 months).

Hemodynamic Variables

In the intervention group, resting heart rate decreased from 74 ± 11 to 68 ± 10 beats per minute ($p < 0.05$), whereas systolic resting blood pressure remained unchanged (128 ± 19 versus 129 ± 18 mm Hg) (Table 6). Physical work capacity increased by 23% from 159 ± 53 W to 195 ± 51 W ($p < 0.0001$), $\dot{V}O_{2\text{max}}$

TABLE 4. Results of 24-Hour Dietary Protocols

Variable	Baseline	Average	Change (%)
Intervention			
Energy consumption (kcal/24 hr)	2,117 \pm 589	1,540 \pm 499*	-577 \pm 600 (-27)
Total fat consumption (g/24 hr)	95 \pm 43	45 \pm 13*†	-50 \pm 43† (-53)
Cholesterol consumption (mg/24 hr)	355 \pm 178	135 \pm 52*†	-220 \pm 183† (-62)
Carbohydrate consumption (g/24 hr)	187 \pm 52	196 \pm 79	+9 \pm 75 (+5)
Control			
Energy consumption (kcal/24 hr)	2,014 \pm 813	1,638 \pm 486*	-376 \pm 694 (-19)
Total fat consumption (g/24 hr)	83 \pm 44	62 \pm 28*	-21 \pm 40 (-25)
Cholesterol consumption (mg/24 hr)	357 \pm 212	232 \pm 139*	-125 \pm 215 (-35)
Carbohydrate consumption (g/24 hr)	189 \pm 76	182 \pm 52	7 \pm 74 (-4)

Average, mean for total study period.

*Significant difference baseline vs. average ($p < 0.05$, Wilcoxon signed rank test).

†Significant difference intervention vs. control ($p < 0.05$, ANOVA).

TABLE 5. Metabolic Variables

Variable	Baseline	3 Weeks	3 Months	6 Months	9 Months	12 Months	Average	Change (%)
Intervention								
Body mass index (kg/m ²)	26.7±2.5	25.8±2.3	25.4±2.6	25.5±2.7	25.3±2.7	25.1±2.9	25.4±2.8*	-1.3±1.0† (-5)
Cholesterol (mmol/l)	6.05±1.00	4.62±0.85	5.46±0.98	5.73±1.05	5.69±0.98	5.74±1.10	5.44±0.87*†	-0.61±0.83† (-10)
HDL (mmol/l)	0.92±0.24	0.85±0.21	0.93±0.27	0.96±0.29	0.97±0.26	1.01±0.31	0.94±0.23	+0.02±0.15 (+3)
LDL (mmol/l)	4.24±0.69	3.19±0.87	3.91±0.80	4.09±0.89	4.07±0.75	4.07±0.86	3.85±0.70*	-0.39±0.60† (-8)
CHOL/HDL	6.87±1.62	5.73±1.57	6.23±1.81	6.41±1.98	6.26±1.97	6.05±1.73	6.14±1.62*†	-0.73±0.90† (-11)
Triglycerides (mmol/l)	1.97±0.81	1.21±0.46	1.48±0.68	1.61±0.89	1.58±0.83	1.64±0.86	1.50±0.61*†	-0.47±0.53† (-24)
Control								
Body mass index (kg/m ²)	26.4±2.2	26.1±2.2	26.3±2.5	26.4±2.5	26.6±2.5	26.2±2.5	26.3±2.4	+0.03±0.8 (±0)
Cholesterol (mmol/l)	6.09±1.03	5.88±0.96	6.11±0.96	6.22±0.91	6.02±0.94	6.08±1.04	6.10±0.77	+0.05±0.60 (±0)
HDL (mmol/l)	0.91±0.18	0.82±0.19	0.92±0.18	0.96±0.19	0.91±0.17	0.94±0.18	0.91±0.14	+0.00±0.13 (±0)
LDL (mmol/l)	4.25±0.85	4.31±0.94	4.31±0.85	4.44±1.00	4.31±0.83	4.37±0.87	4.34±0.80	+0.09±0.39 (+2)
CHOL/HDL	6.85±1.47	7.51±1.75	6.81±1.34	6.62±1.25	6.77±1.39	6.61±1.44	6.97±1.10	+0.12±1.16 (+2)
Triglycerides (mmol/l)	2.16±1.24	1.54±0.57	1.89±0.84	1.93±0.98	1.82±0.88	1.79±0.76	1.80±0.68*	-0.36±1.03 (-17)

Average, mean for total study period (3 weeks, 3, 6, 9, 12 months); HDL, high density lipoproteins; LDL, low density lipoproteins; CHOL, total cholesterol.

*Significant difference baseline vs. average ($p < 0.05$, Wilcoxon signed ranks test).

†Significant difference intervention vs. control ($p < 0.05$, ANOVA).

from 1.8 ± 0.4 l/min to 2.0 ± 0.4 l/min ($p < 0.05$), maximal heart rate from 142 ± 17 to 148 ± 17 beats per minute, and maximal systolic blood pressure from 188 ± 24 to 198 ± 22 mm Hg ($p < 0.05$); consequently, maximal rate-pressure product rose by +10% from $26.9 \pm 5 \times 10^3$ to $29.5 \pm 5 \times 10^3$ ($p < 0.05$) (Figure 2). At 12 months, resting heart rate, physical work capacity, maximal oxygen uptake, maximal systolic blood pressure, and maximal rate-pressure product differed significantly from the corresponding variables in the control group. In the control group, all hemodynamic variables remained essentially unchanged. (Also see Table 7.)

²⁰¹Tl Scintigraphy

Intervention group. Immediately after termination of exercise, the size of the ²⁰¹Tl perfusion measured $59 \pm 54^\circ$; after redistribution, it had decreased to $14 \pm 29^\circ$ (Table 6). Therefore, stress-induced reversible ²⁰¹Tl

ischemia was calculated to be $44 \pm 44^\circ$ at baseline. At 12 months, the corresponding values were $50 \pm 47^\circ$, $10 \pm 20^\circ$, and $39 \pm 40^\circ$ (significantly different from baseline, $p < 0.05$).

Control group. At baseline, the size of the perfusion defect immediately after exercise was $61 \pm 60^\circ$ and after redistribution was $19 \pm 23^\circ$. Reversible stress-induced ²⁰¹Tl ischemia was calculated to be $42 \pm 37^\circ$. At 12 months, the corresponding values were $62 \pm 61^\circ$, $22 \pm 28^\circ$, and $41 \pm 44^\circ$.

To assess the effect that progression or regression of coronary lesions had on myocardial hemodynamics, both groups were combined. In patients with progression, maximal rate-pressure product decreased significantly ($-1.96 \pm 6.6 \times 10^3$) compared with patients with no change ($+1.71 \pm 4.85 \times 10^3$) or regression ($+1.74 \pm 7.56 \times 10^3$, $p < 0.05$) in whom an increase was noted. Similarly, the extent of stress-induced myocardial ischemia tended to decrease in patients with regression ($-9 \pm 35^\circ$) or no change ($-8 \pm 24^\circ$), whereas an increase was noted in patients with progression ($+7 \pm 41^\circ$); these differences, however, did not reach statistical significance ($p < 0.2$).

The end points for terminating the stress test are listed in Table 5. At 12 months, the number of positive ECGs in the intervention group had decreased significantly compared with the control group ($p < 0.05$), and fewer patients stopped as a result of progressive angina pectoris ($p = 0.06$).

Blood Rheology

In the intervention group, erythrocyte aggregation rate decreased by 18%, from 0.34 ± 0.11 Pa to 0.28 ± 0.07 Pa ($p < 0.002$) and in the control group from 0.35 ± 0.10 Pa to 0.31 ± 0.07 Pa ($p < 0.05$); at 12 months, both groups were significantly different from each other ($p < 0.05$).

Coronary Morphology

In 92 patients, follow-up angiograms were available at 12 months (intervention, $n = 40$; control, $n = 52$). An average of 3.05 (range, 1–7) stenoses were evaluated in each patient.

Intervention group: Evaluation on per-patient basis. According to minimal diameter reduction, the incidence of progression noted in 23% of patients, no change in

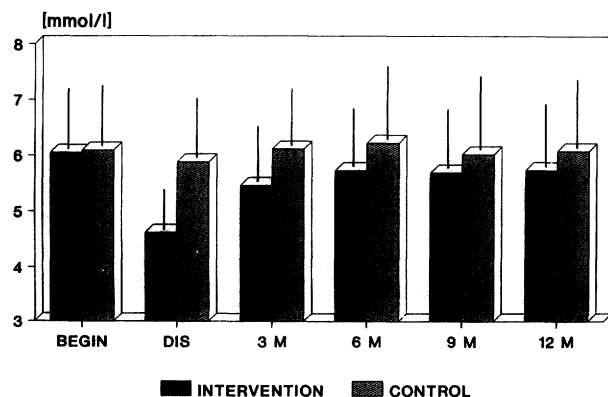


FIGURE 1. Graph of temporal change of total serum cholesterol levels. Initial levels were only marginally elevated; during strict supervision on the metabolic ward, a decrease of 23% was noted in the intervention group. In the following months, part of this satisfactory result was lost, and average reduction throughout the year amounted to 10%. Cholesterol levels in the control group remained essentially unchanged. After initiation of therapy, both groups differed significantly from each other ($p < 0.05$). DIS, discharge from the metabolic ward after the initial 3 weeks.

TABLE 6. Hemodynamic and Scintigraphic Variables

Variable	Baseline	12 Months	Change (%)
Intervention			
Resting heart rate (bpm)	74±11	68±10†	-8†
Resting systolic blood pressure (mm Hg)	128±19	129±18	±0
Maximal heart rate (bpm)	142±17	149±17*	+4†
Maximal systolic blood pressure (mm Hg)	188±24	198±22*‡	+5†
Physical work capacity (W)	159±53	195±51§†	+23‡
Maximal oxygen uptake (l/min)	1.8±0.4	2.0±0.4*	+12†
Maximal rate–pressure product (*10 ³)	26.9±5	29.5±5§†	+10†
²⁰¹ Tl perfusion defect, exercise	59±54°	50±47°	-15
²⁰¹ Tl perfusion defect, redistribution	14±29°	10±20°	-28
²⁰¹ Tl perfusion defect, difference	44±44°	39±40°*	-10
Control			
Resting heart rate (bpm)	76±12	76±12	±0
Resting systolic blood pressure (mm Hg)	128±21	128±18	±0
Maximal heart rate (bpm)	151±20	149±19	-1
Maximal systolic blood pressure (mm Hg)	190±27	184±20	-3
Physical work capacity (W)	163±47	173±53	+6
Maximal oxygen uptake (l/min)	1.9±0.5	1.9±0.5	±0
Maximal rate–pressure product (*10 ³)	28.6±6	27.4±5	-4
²⁰¹ Tl perfusion defect, exercise	61±60°	62±61°	+2
²⁰¹ Tl perfusion defect, redistribution	19±23°	22±28°	16
²⁰¹ Tl perfusion defect, difference	42±37°	41±44°	-2

bpm, Beats per minute; ²⁰¹Tl perfusion defect, exercise, perfusion defect immediately after termination of exercise (degrees of left difference ventricular circumference); ²⁰¹Tl perfusion defect, redistribution, perfusion defect 4 hours after termination of exercise; ²⁰¹Tl perfusion defect, difference, stress-induced, reversible perfusion defect (Δ exercise–redistribution).

*Significantly different baseline vs. 12 months ($p < 0.05$).

†Significantly different intervention vs. control ($p < 0.05$).

‡Significantly different intervention vs. control ($p < 0.0005$).

§Significantly different baseline vs. 12 months ($p < 0.005$).

45%, and regression in 32% (Table 8, Figure 3). There were six new lesions in previously normal coronary segments; four in previously open vessels progressed to total occlusion, and four totally occluded segments were recanalized. According to relative diameter reduction, progression was noted in 20% of patients, no change in 50%, and regression in 30%.

Evaluation on per-lesion basis. No significant change was noted either in relative diameter reduction ($65 \pm 24\%$ versus $64 \pm 23\%$) or minimal diameter reduction (0.92 ± 0.72 mm versus 0.91 ± 0.67 mm) (Table 9, Figure 4).

Control group: Evaluation on per-patient basis. According to minimal diameter reduction, the incidence of progression was noted in 48% of patients, no change in 35%, and regression in 17% (Table 8, Figure 3). There were seven new lesions, seven previously open vessels occluded, and five totally occluded vessels were recanalized. With respect to relative diameter reduction,

TABLE 7. Results of ECG Stress Testing

Reasons for terminating stress test	Baseline (No.) (%)*	12 Months (No.) (%)*
Intervention		
Fatigue	11 (31)	19 (53)
Progressive angina	22 (61)	17 (47)
ST segment depression	15 (44)	8 (24)†
Control		
Fatigue	25 (53)	23 (49)
Progressive angina	21 (45)	21 (45)
ST segment depression	13 (30)	15 (35)

*Cumulative percentage amounts with >100%, as patients may have more than one reason for terminating exercise.

†Significant change compared with control ($p < 0.05$).

progression was noted in 42% of patients, no change in 54%, and regression in 4%. For both methods (i.e., relative diameter reduction [$p < 0.001$] and absolute minimal diameter [$p < 0.05$]), a statistically significant difference was detected between both groups.

Evaluation on per-lesion basis. The per-lesion analysis showed significant progression of coronary lesions with respect to relative diameter reduction ($63 \pm 29\%$ versus $66 \pm 28\%$, $p < 0.005$) and minimal diameter reduction

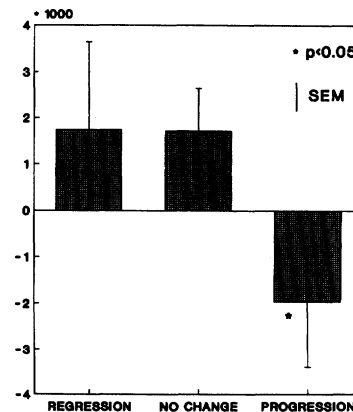


FIGURE 2. Graph of change of maximal rate–pressure product according to change of coronary morphology. To analyze the effect of progression or regression of coronary lesions on maximal myocardial oxygen consumption, both groups were combined. In patients with regression or no change, maximal rate–pressure product increased at 12 months, whereas in patients with progression, a significant deterioration was observed.

TABLE 8. Change in Coronary Morphology With Evaluation on Per-Patient Basis

	Relative diameter reduction* (No.) (%)	No. (%)	Minimal diameter reduction† (No.) (%)
Intervention (n=40)			
Progression	8 (20)		9 (23)
No change	20 (50)		18 (45)
Regression	12 (30)		13 (32)
New lesions		6 (15)	
New occlusions		4 (10)	
Recanalization		4 (10)	
Control (n=52)			
Progression	22 (42)		25 (48)
No change	28 (54)		18 (35)
Regression	2 (4)		9 (17)
New lesions		7 (14)	
New occlusions		7 (14)	
Recanalization		5 (10)	

* $p < 0.001$ vs. control group.† $p < 0.05$ vs. control group.

(1.00 ± 0.87 mm versus 0.87 ± 0.79 mm, $p < 0.05$). Changes were significantly different versus intervention ($p < 0.05$) (Table 9, Figure 4).

Although patients with regression tended to have lower cholesterol levels after initiation of therapy (5.62 ± 0.96 mmol/dl [217 ± 37 mg/dl]) compared with patients with no change (5.72 ± 0.80 mmol/l [221 ± 31 mg/dl]) and patients with progression (5.98 ± 0.93 mmol/l [231 ± 36 mg/dl]), these differences did not reach statistical significance ($p = 0.36$). Similarly, the intensity of physical activity, as assessed by participation in group training sessions, was not significantly correlated to changes in coronary morphology.

Psychological Changes

On the basis of psychological assessment, patients recruited for the study did not differ significantly from patients not willing to participate in either study group. There was a slight but insignificant trend for the partic-

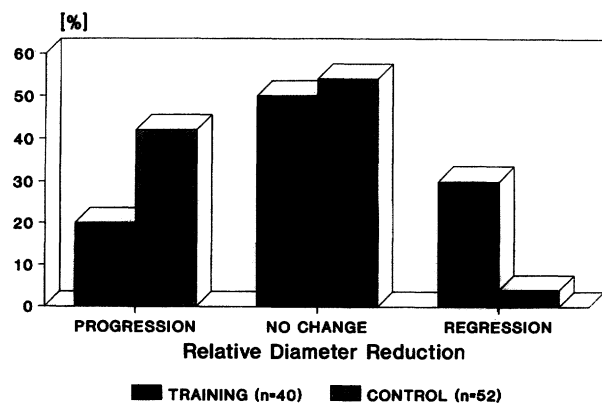


FIGURE 3. Graph of change in coronary morphology (based on individual patients and relative diameter reduction). In the intervention group, regression was noted in 30% of patients, no change in 50%, and progression in 20%. In the control group, coronary morphology deteriorated in 42%, no change was noted in 54%, and regression was noted in 4%. Both groups differed significantly from each other ($p < 0.001$).

TABLE 9. Change in Coronary Morphology With Evaluation on Per-Lesion Basis

	Begin	12 Months	Change
Intervention (122 lesions; 3.05 lesions/patient)			
Relative diameter reduction (%)	65 ± 24	64 ± 23	-1 ± 13
Minimal diameter (mm)	0.92 ± 0.72	0.91 ± 0.67	0.0 ± 0.38
Control (158 lesions; 3.04 lesions/patient)			
Relative diameter reduction (%)	63 ± 29	$66 \pm 28^*$	$+3 \pm 13^\dagger$
Minimal diameter (mm)	1.00 ± 0.87	$0.87 \pm 0.79^*$	$-0.13 \pm 0.45^\dagger$

* $p < 0.005$ vs. 12 months.† $p < 0.05$ vs. control.

ipants to have a more internally oriented health locus-of-control score (participants, 22.2 ± 5.1 ; rejectors, 20.2 ± 5.7 ; $p < 0.20$). A significant change was detected in the intervention group on one of the health locus-of-control scales: Patients' personal-external orientation decreased from 22.8 ± 5.4 to 20.8 ± 5.2 ($p < 0.05$); at the same time, the control group's tended to increase (21.9 ± 6.5 versus 23.2 ± 6.0 , $p > 0.30$), resulting in a significant interaction effect ($p < 0.05$). With respect to the degree of depression, no significant changes could be observed in either group (intervention, 7.7 ± 5.8 versus 7.5 ± 6.4 ; $p > 0.90$; control, 5.1 ± 4.9 versus 6.9 ± 6.0 ; $p > 0.10$).

Discussion

Metabolic Changes

Individuals recruited for this intervention program constitute a representative sample of the large number of patients suffering from coronary artery disease. Patients participating in the intervention group were requested to follow a dietary schedule based the American Heart Association's recommendation phase 3.³⁰ On their dietary protocols, all patients reported satisfactory reduction of total energy consumption by -25% , total fat consumption by -53% , and cholesterol intake by

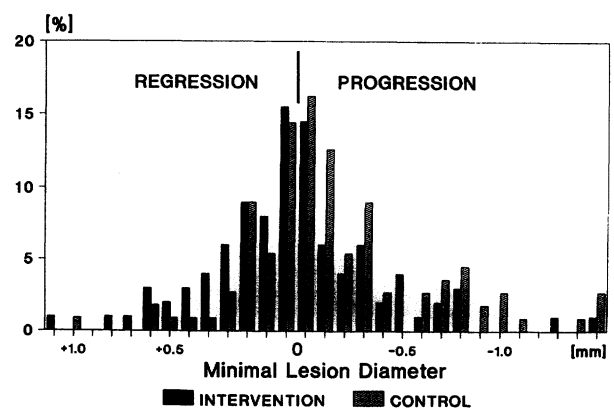


FIGURE 4. Graph of change in coronary morphology (based on individual stenoses and minimal diameter). Minimal lesion diameter is shown on the abscissa, percentage of lesions on the ordinate. There is approximately equal distribution of lesions on both sides of 0 (no change) for the intervention group. For the control group, the distribution is shifted to the right (progression).

–64%. During the initial period of strict supervision on the metabolic ward, these changes were reflected by a corresponding drop in serum lipoprotein levels (Figure 1, Table 4). In the following months, there was a considerable erosion of dietary discipline; average reductions of lipoproteins were far from those achieved during strict supervision on the metabolic ward (Table 5). Moreover, they did not nearly approach the expectations based on the evaluation by dietary protocols. Reductions of serum lipoprotein levels, which can be achieved by drug therapy or in an experimental setting, are considerably greater. In patients treated with lovastatin and colestipol (FATS study), total cholesterol decreased by 46%, and HDL increased by 15%.² In the Lifestyle Heart Trial, selected and well-motivated patients were asked to consume a strictly vegetarian diet limiting cholesterol intake to 5 mg per day. In these patients, total cholesterol decreased by 24%, LDL by 37%, and HDL by 3%, whereas triglycerides increased by 22%.⁹ In everyday clinical practice, only a very small minority of patients are willing and capable of following such stringent and austere schedules; the vast majority shirks away from unrealistic expectations. Patients participating in the present study were not endowed with exceptional motivation and compliance; they were representative of the average individual with coronary artery disease coming to medical attention.

Hemodynamic Variables and Myocardial Perfusion

Group training sessions proved to be an important incentive to maintain a high level of physical activity. The compliance rate of 68%, which does not take into account all physical exercise that patients performed on their own or during vacation times, suggests that most patients find it more attractive to participate in sports programs than to follow dietary guidelines.

The increase in maximal rate–pressure product in the face of decreased stress-induced myocardial ischemia suggests that the effect of regular physical exercise extends to myocardial mechanics and coronary circulation, a finding supported by several other studies (Table 6).^{34–40} The strictly aerobic pattern of cardiac metabolism, and the near maximal oxygen extraction, even during basal conditions, precludes the use of adaptive changes encountered in skeletal muscle. An increase in peak maximal oxygen uptake is therefore effected by changes in coronary blood flow.⁴¹ Several mechanisms have been implicated by which myocardial perfusion during maximal stress may be augmented: regression of coronary lesions, an increase in collateral circulatory capacity,^{42,43} and improvement of blood rheology.^{44,45}

Improvement of maximal rate–pressure product and stress-induced myocardial ischemia in patients with regression of coronary lesions emphasizes the importance of this mechanism (Figure 2); however, no net regression of coronary lesions was observed in the intervention group; moreover, a decrease in myocardial ischemia was not limited to patients with regression but also occurred in individual patients with no change or significant progression. Therefore, alternative mechanisms will probably contribute to the improvement of myocardial perfusion. Recruitment of preformed collateral channels during maximal exercise may represent a second mechanism; angiographic studies performed in humans at rest, however, have failed to substantiate this hypothesis.^{46,47}

Possibly, these channels are utilized only during physical stress; therefore, angiographic images obtained during exercise might yield different results. Normalization of blood rheology in patients with occlusive peripheral artery disease has been shown to increase calf blood flow consistently.⁴⁸ In this study, erythrocyte aggregation rate decreased by 18% ($p < 0.002$), resulting in improved blood fluidity; the contribution of this mechanism to the reduction of stress-induced myocardial ischemia, however, remains to be determined.

Change in Coronary Morphology

Angiograms obtained after 12 months of intensive exercise and low-fat diet did not show predominant regression of coronary lesions. If statistical evaluation was based on individual lesions, no change was noted with respect to relative diameter reduction or minimal diameter (Tables 8 and 9, Figures 3 and 4). Therefore, this form of treatment resulted in no detectable progression of disease on the average within the observation period. In patients on usual care, however, there was considerable progression of disease; significant minimal diameter reduction was observed in 48% of patients, whereas an increase in luminal width was noted in only 17%. Nearly identical rates of progression were observed by Kramer⁴⁹ (47%) and Brusckhe⁵⁰ (40%) in patients who were recatheterized within 1 year and who did not receive any specific treatment during that time.

Combined colestipol-niacin therapy in patients after aortocoronary bypass surgery resulted in significant reduction in the average number of lesions that progressed per subject and in the percentage of subjects with new lesions.¹ Average global score, however, remained unchanged in the treatment group, whereas progression was noted in the placebo group. Only compliant and responsive subjects were selected for this study in a prerandomization trial. In another study² of similar design, lovastatin, niacin, and colestipol were used as lipid-lowering therapy in men with high levels of apolipoprotein B. Contrary to our study and the results of the CLAS study, there was predominant and significant regression of proximal coronary lesions in patients on lovastatin and colestipol (average minimal diameter, +0.012 mm) and in patients on niacin/colestipol (average minimal diameter, +0.035 mm). Predominant progression was noted in the control group (average minimal diameter, –0.05 mm).

In the Lifestyle Heart Trial,⁹ 82% of all patients participating in the intervention group showed predominant regression of coronary atherosclerosis, and changes in lesions were strongly related to the overall adherence to lifestyle changes. Those patients who made the greatest changes showed the greatest improvement. Quite unexpectedly, 42% of the patients in the control group also showed coronary changes in the direction of regression.

In the present study, even excellent adherence to the guidelines did not invariably guarantee immunity from an adverse course; progression was observed in individual patients with dietary and exercise compliance far above the group average (LDL < 2.6 mmol/l [100 mg/dl], HDL > 1.5 mmol/l [60 mg/dl], heavy physical activity > 10 hr/wk). On the other hand, patients with only moderate ambition and less-than-ideal results may

experience significant benefit with arrest or even regression of coronary lesions.

Clinical Events

There were several clinical events in both study groups (Table 2). Two of the cardiac arrests were clearly related to physical exercise, but only one occurred during a group training session. Details and circumstances of the unwitnessed cardiac arrest in the third case (patient 40) could not be ascertained and, therefore, are not attributable to exercise. Three patients developed life-threatening arrhythmias during the initial exercise session; they were excluded from further participation and subsequently underwent electrophysiological testing and antiarrhythmic treatment.

Physical exercise has been shown to be relatively safe during supervised training sessions.⁵¹ However, well-motivated patients, in particular, are at great risk to exceed their recommended target heart rates. Otherwise correctable arrhythmias frequently bear grave consequences whenever they occur during unsupervised exercise.^{52,53} Patients at highest risk of cardiac arrest during cardiac rehabilitation are those having marked ischemia on an exercise ECG, an above-average exercise capacity, and a record of poor compliance with exercise intensity guidelines.^{54,55} In all three patients, Holter monitor tapes obtained during previous group training sessions were available and showed heart rates above the recommended individual limit. One of these patients (patient 104) happened to undergo Holter monitoring at the time of cardiac arrest; heart rates exceeding 130% of the recommended target rate were documented immediately before the episode. An identical case was observed by Ornish⁹ in a patient who also exceeded his training recommendation during unsupervised exercise. No other factor, such as severity of coronary artery disease, left ventricular pump function, or degree of stress-induced myocardial ischemia could be identified as predictive in these patients.

Implications for Clinical Practice

The message contained in the results of this study is threefold: First, the course of coronary artery disease is amenable to dietary reduction of serum lipoproteins and regular physical exercise. Although there was no net regression of atherosclerotic lesions, coronary artery disease progressed at a significantly slower pace as compared with the control group. No clear-cut, linear relation was detected between patient compliance and directional changes of coronary lesions. Improvement of physical work capacity, myocardial oxygen consumption, and reduction of stress-induced myocardial ischemia was observed in nearly all patients participating in the intervention group. As improvement of myocardial perfusion was not limited to patients with regression of coronary lesions, other mechanisms, such as collateral circulation and blood rheology, may be operative in these patients. With respect to psychological changes, two aspects are noteworthy: Patients achieve a greater degree of mental independence from outside control of their physical well-being, and they tend to be less depressive than their counterparts in the control group. Second, intensive physical exercise is associated with an increased risk of cardiac arrest, particular in well-motivated, young patients, who frequently exceed their

training recommendations not only during supervised group training sessions but also while exercising on their own. The risk of life-threatening arrhythmias inherently associated with this form of therapy needs to be carefully weighed against the benefit of less progression of coronary disease, improved physical work capacity, and reduced myocardial ischemia. Use of continuous heart rate monitoring by a portable device may contribute to increased security for these patients.⁵¹ Frequent counseling about the rules and risks of physical exercise remains an important adjunct to this form of rehabilitation. Third, observations in the control group suggest that present-day clinical practice (i.e., usual care) is largely unsuccessful in modifying certain risk factors or in affecting the unrelenting course of coronary artery disease. It is such current knowledge as this that we believe the medical profession should be challenged to better communicate to their patients.

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References

- Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L: Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;257:3233-3240
- Brown G, Albers JJ, Fisher LD, Schaefer SM, Lin JT, Kaplan C, Zhao XQ, Bisson BD, Fitzpatrick VF, Dodge HT: Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289-1298
- Blankenhorn DH, Azen SP, Crawford DW, Nessim SA, Sanmarco ME, Selzer RH, Shircore AM, Wickham EC: Effects of colestipol-niacin therapy on human femoral atherosclerosis. *Circulation* 1991; 83:438-447
- Nikkilä EA, Viikinkoski P, Valle M, Frick MH: Prevention of progression of coronary atherosclerosis by treatment of hyperlipidemia: A seven year prospective angiographic study. *Br Med J* 1984;289:220-223
- Brensike JF, Levy RI, Kelsey SF, Passamani ER, Richardson JM, Loh IK, Stone NJ, Aldrich RF, Battaglini JW, Moriarty DJ, Fisher MR, Friedman L, Friedewald W, Detre KM, Epstein SE: Effects of therapy with cholestyramine on progression of coronary atherosclerosis: Results of the NHLBI type II coronary intervention study. *Circulation* 1984;69:313-324
- Buchwald H, Varco RL, Matts JP, Long JM, Fitch LL, Campbell GS, Buchwald H, Varoo RL, Matts JP, Long JM, Fitch LL, Campbell GS, Pearce MB, Yellin AE, Edmiston WA, Smink RD, Sawin HS Jr, Campos CT, Hansen BJ, Tuna N, Karnegis JN, Sanmarco ME, Amplatz K, Castaneda-Zuniga WR, Hunter W, Bissett JK, Weber FJ, Stevenson JW, Leon AS, Chalmers TC, and the POSCH Group: Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. *N Engl J Med* 1990;323:946-955
- Schuler G, Schlierf G, Wirth A, Mautner HP, Scheurlen H, Thumm M, Roth H, Schwarz F, Kohlmeier M, Mehmel HC, Kübler W: Low-fat diet and regular, supervised physical exercise in patients with symptomatic coronary artery disease: Reduction of stress-induced myocardial ischemia. *Circulation* 1988;77:172-181
- Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ: Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens. *JAMA* 1990;264:3007-3012
- Ornish D, Brown SE, Scherwitz LW, Billings JH, Armstrong WT, Ports TA, McLanahan SM, Kirkeeide RL, Brand RJ, Gould KL: Can lifestyle changes reverse coronary heart disease? *Lancet* 1990; 2:129-133
- Nikolaus T, Schlierf G, Vogel G, Schuler G, Wagner I: Treatment of coronary artery disease with diet and exercise: Problems of compliance. *Ann Nutr Metab* 1991;35:1-7

11. Brown BG, Bolson E, Frimer M, Dodge HT: Quantitative coronary angiography, estimation of dimensions, hemodynamic resistance, and atheroma mass of coronary artery lesions using the arteriogram and digital computation. *Circulation* 1977;55:329-337
12. Reiber JHC, Serruys PW, Kooijman CJ, Wijns W, Slager CJ, Gerbrands JJ, Schuurbijs JCH, Boer AD, Hugenholtz PG: Assessment of short-, medium-, and long-term variations in arterial dimensions from computer-assisted quantification of coronary cineangiograms. *Circulation* 1984;71:280-288
13. Gould KL: Quantification of coronary artery stenosis in vivo. *Circ Res* 1985;57:341-353
14. Singh RN: Progression of coronary atherosclerosis: Clues to pathogenesis from serial coronary arteriography. *Br Heart J* 1984;52:451-461
15. Wolthuis RA, Froelicher VF, Fisher J, Noguera I: New practical treadmill protocol for clinical use. *Am J Cardiol* 1977;39:97-100
16. Gobel FL, Nordstrom LA, Nelson RR, Jorgenson CR, Wang Y: The rate-pressure product as an index of myocardial oxygen consumption during exercise in patients with angina pectoris. *Circulation* 1978;57:549-555
17. Laslett LJ, Paumer L, Amsterdam EA: Increased myocardial oxygen consumption indexes by exercise training at onset of ischemia in patients with coronary artery disease. *Circulation* 1985;71:958-962
18. Vogel RA, Kirch DL, LeFree MT, Rainwater JO, Jensen DP, Steele PP: Thallium-201 myocardial perfusion scintigraphy: Results of standard and multi-pinhole tomographic techniques. *Am J Cardiol* 1979;43:787-792
19. Vogel RA, Kirch DL, LeFree M, Steele PP: A new method of multiplanar emission tomography using a seven pinhole collimator and an Anger scintillation camera. *J Nucl Med* 1978;19:648-652
20. Ritchie JL, Williams DL, Caldwell JH, Stratton JR, Harp GD, Vogel RA, Hamilton GW: Seven-pinhole emission tomography with thallium-201 in patients with prior myocardial infarction. *J Nucl Med* 1981;22:107-112
21. Schuler G, Schwarz F, Hofmann M, Mehmel HC, Manthey J, Mäurer W, Rauch B, Herrmann HJ, Kübler W: Thrombolysis in acute myocardial infarction using intracoronary streptokinase: Assessment by thallium-201 scintigraphy. *Circulation* 1982;66:658-664
22. Schuler G, Hofmann M, Schwarz F, Mehmel HC, Manthey J, Tillmanns H, Hartmann S, Kübler W: Effect of successful thrombolytic therapy on right ventricular function in acute inferior myocardial infarction. *Am J Cardiol* 1984;54:951-957
23. Lipid Research Clinics Program: *Manual of Laboratory Operations*. US Dept of Health, Education, and Welfare publication No. (NIH) 75-628. Washington, DC, US Government Printing Office, 1974
24. Praxisorientiertes Dialogsystem für Ernährungs- und Diätberatung (PRODI III), Stuttgart, Wissenschaftliche Verlagsgesellschaft mbH, 1991
25. Harkness J: A new instrument for the measurement of plasma viscosity. *Lancet* 1963;2:280-281
26. Volger E, Schmid-Schönbein H, VonGosen J, Klose HJ, Kline KA: Microrheology and light transmission of blood: IV. The kinetics of artificial red cell aggregation induced by dextran. *Pflugers Arch* 1975;354:319-337
27. Neumann FJ, Schmid-Schönbein H, Ohlenbusch H: Temperature-dependence of red cell aggregation. *Pflugers Arch* 1987;408:524-530
28. Wallston KA, Wallston BS, DeVellis R: Development of the multidimensional health locus of control (MHLC) scales. *Health Education Monographs* 1978;6:160-170
29. vZerssen D: *Depressivitäts-Skala*. Weinheim, Beltz, 1975
30. American Heart Association Special Report: Recommendations for the treatment of hyperlipidemia in adults. *Circulation* 1984;69:1065A
31. Sachs L: *Angewandte Statistik*, 6. Aufl., Berlin, Springer Verlag, 1984
32. Ashley FA, Kannel WB: Relation of weight change to changes in atherogenic trait: The Framingham study. *J Chronic Dis* 1974;27:103-114
33. Gensini GG: *Coronary Angiography*. Mount Kisco, NY, Futura Publishing Co, 1975, p 272
34. Clausen JP: Circulatory adjustments to dynamic exercise and the effect of physical training in normal subjects and in patients with coronary artery disease. *Prog Cardiovasc Dis* 1976;18:459-495
35. Kennedy CC, Spiekerman RE, Lindsay MI, Mankin HT, Frye RL, McCallister BD: One-year graduated exercise program for men with angina pectoris. *Mayo Clin Proc* 1976;51:231-236
36. Froelicher V, Jensen D, Genter F, Sullivan M, McKirnan MD, Witzum K, Scharf J, Strong ML, Ashburn W: A randomized trial of exercise training in patients with coronary artery disease. *JAMA* 1984;252:1291-1297
37. Ehsani AA, Heath GW, Hagberg JM, Sobel BE, Holloszy JO: Effects of 12 months intense exercise training on ischemic ST segment depression in patients with coronary artery disease. *Circulation* 1981;64:1116-1124
38. Redwood DR, Rosing DR, Epstein SE: Circulatory and symptomatic effects of physical training in patients with coronary artery disease and angina pectoris. *N Engl J Med* 1972;286:959-965
39. Sim DN, Neill WA: Investigation of the physiological basis for increased exercise threshold for angina pectoris after physical conditioning. *J Clin Res* 1974;54:763-770
40. Amsterdam EA, Hughes JL III, DeMaria AN: Indirect assessment of myocardial oxygen consumption in the evaluation of mechanisms and therapy of angina pectoris. *Am J Cardiol* 1974;33:737-743
41. Kitamura K, Jorgensen CR, Gobel F: Hemodynamic correlates of myocardial oxygen consumption during upright exercise. *J Appl Physiol* 1972;32:516-522
42. Leon AS, Bloor CM: Effects of exercise and its cessation on the heart and its blood supply. *J Appl Physiol* 1968;24:485-490
43. Heaton WH, Marr KC, Capurro NL, Goldstein RE, Epstein SE: Beneficial effect of physical training on blood flow to myocardium perfused by chronic collaterals in the exercising dog. *Circulation* 1978;57:575-582
44. Ernst EEW, Matri A: Intermittent claudication, exercise, and blood rheology. *Circulation* 1987;76:1110-1114
45. Most AS, Ruocco NA, Gewirtz H: Effect of a reduction in blood viscosity on maximal myocardial oxygen delivery distal to a moderate coronary stenosis. *Circulation* 1986;74:1085-1092
46. Nolewajka AJ, Kostuk WJ, Rechnitzer PA, Cunningham DA: Exercise and human collateralization: An angiographic and scintigraphic assessment. *Circulation* 1979;60:114-121
47. Ferguson RJ, Petitclerc R, Choquette G, Chaniotis L, Gauthier P, Huot R, Allard C, Jankowski L, Campeau L: Effect of physical training on treadmill exercise capacity, collateral circulation and progression of coronary disease. *Am J Cardiol* 1974;34:764-769
48. Yates C, Bernet A, Andrews V, Dormandy J: Increase in leg flow by normovolemic hemodilution in intermittent claudication. *Lancet* 1979;2:166-172
49. Kramer JR, Matsuda Y, Mulligan JC, Aronow M, Proudfit WL: Progression of coronary atherosclerosis. *Circulation* 1981;63:519-526
50. Brusckhe AVG, Wijers TS, Kolsters W, Landmann J: The anatomic evolution of coronary artery disease demonstrated by coronary arteriography in 256 nonoperated patients. *Circulation* 1981;63:527-536
51. Haskell WL: Cardiovascular complications during exercise training of cardiac patients. *Circulation* 1978;57:920-924
52. Thompson PD, Funk EJ, Carleton RA, Sturmer WQ: Incidence of death during jogging in Rhode Island from 1975 through 1980. *JAMA* 1982;247:2535-2538
53. Fletcher GF, Cantwell JD: Ventricular fibrillation in medically supervised cardiac exercise program. *JAMA* 1977;238:2627-2629
54. Hossack KF, Hartwig R: Cardiac arrest associated with supervised cardiac rehabilitation. *J Cardiac Rehabil* 1982;2:402-408
55. Cobb LA, Weaver WD: Exercise: A risk for sudden death in patients with coronary artery disease. *J Am Coll Cardiol* 1986;7:215-219