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Myocardial Perfusion and Regression of Coronary Artery Disease in Patients on a Regimen of Intensive Physical Exercise and Low Fat Diet

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This intervention program tested the applicability and effects of intensive physical exercise and a low fat diet on progression of coronary atherosclerotic lesions and stress-induced myocardial ischemia in patients with stable angina pectoris. Eighteen patients participated in this program for 1 year; they consumed a low fat, low cholesterol diet (<20 energy% fat, cholesterol <200 mg/day) and exercised for >3 h/week. Change in coronary morphology was assessed by angiography and digital image processing; stress-induced myocardial ischemia was measured by thallium-201 scintigraphy. Results were compared with those in patients receiving "usual care."

In the intervention group, significant regression of coronary atherosclerotic lesions was noted in 7 of the 18 patients; no change or progression was present in 11 patients. In patients receiving usual care, regression was detected in only 1, with no change or progression in 11 patients (different from intervention, $p < 0.05$). There was a significant reduction in stress-induced myocardial ischemia, which was not limited to patients with regression of coronary atherosclerotic lesions. Thus, regular physical exercise and a low fat diet may retard progression of coronary artery disease; however, improvement of myocardial perfusion may be achieved independently from regression of stenotic lesions.

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Observational reports (1,2) published in recent years suggest that atherosclerotic lesions occasionally may regress spontaneously or in response to normalization of atherogenic factors. This concept has been expanded in controlled intervention studies (3–7), with rigorous reduction in serum lipoproteins by lipid-lowering drugs, vegetarian diet or physical exercise in selected, motivated patients. Whenever demanding and austere programs are advocated for nonselected patients, dropout rates are high and therapeutic failures due to noncompliance are frequent. The present study tested the applicability and effects of the combined restriction of dietary fat consumption, intensive physical exercise and elimination of other risk factors such as smoking and hypertension in a nonselected group of patients endowed with no more than average motivation and self-discipline. Effects on coronary morphology were assessed by quantitative angiography and correlated with functional hemodynamic variables obtained by thallium-201 scintigraphy. Metabolic changes achieved by this form of therapy were discussed previously (8).

Methods

Patient selection. 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 ≥12 months and coronary artery stenoses well documented by angiography. To facilitate regular and frequent participation in group exercise sessions, patients living within 20 km of Heidelberg were assigned to the intervention group, whereas patients living beyond this radius were included in the control group. Matched pairs were created on the basis of age and severity of coronary artery disease (Gensini score) (9). The study was approved by the Human Subject Protection Committee; informed consent was in accordance with the committee's guidelines.

Exclusion criteria were unstable angina pectoris, left main coronary artery stenosis >25% reduction in lumen diameter, severely depressed left ventricular ejection fraction (<35%), significant valvular heart disease, insulin-dependent diabetes mellitus, primary hypercholesterolemia (type II hyperlipoproteinemia, low density lipoprotein >210 mg/dl) and conditions precluding regular physical exercise.

Because selection criteria were numerous and stringent, such as the distance a patient had to travel to reach the training facilities, only 1 in 10 patients with suitable coronary morphology was eligible for the study; the response rate in these patients was 40%.

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Cardiac catheterization. This was performed by the femoral approach; left ventriculography in two orthogonal projections was followed by coronary angiography performed according to the Judkins technique. A minimum of six standard projections was obtained, 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. No vasoactive drugs (nitroglycerin or calcium channel blockers) were used during either catheterization.

Digital image processing. Evaluation of coronary angiograms was performed by two technicians who did not know the sequence of films, the patient's identity or group assignment. Films were viewed in pairs with use of two 35-mm cineangiographic projectors (Vanguard Instruments). Each segment of the coronary tree was examined carefully for changes in lumen diameter. After identification of stenoses, corresponding projections were lined up near end-diastole; both regions of interest containing the stenotic segment were magnified 2.5-fold 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. Because all images were obtained in the 6-in. (15.2-cm) angiographic mode, pincushion distortion was minimal (10,11) and correction was not essential. Coronary vessel boundaries were identified by an automated edge detection algorithm. Minimal stenosis diameter was measured, and percent diameter reduction was calculated by comparing the minimal stenosis diameter with the adjacent normal segments. No attempt was made to calculate atherosclerotic mass because this measurement has demonstrated considerable variability (10,11). As a result of the limited resolution of digital image processing, side branches <1 mm in diameter were not analyzed.

To assess the variability of this method, 25 stenoses were analyzed three times on different days by one technician. The standard deviation between repeated measurements of percent diameter reduction was 4.4%; for minimal diameter, it was 0.25 mm. Consequently, only changes between sequential measurements >10% (2 SD) were considered relevant. Stenoses with <10% change diameter reduction were classified as unchanged (grade ±0). A positive difference of >10% between baseline and end was graded as progression (grade +1) and a negative difference of >10% as regression (grade −1).

In patients with multiple stenoses, the fate of each individual lesion cannot be considered statistically independent; therefore, each patient has to be treated as a statistical unit. Moreover, progression and regression may occur simultaneously in a particular patient. Consequently, for each patient, a single variable was calculated by adding the grades assigned to individual stenoses on the basis of percent diameter reduction. Cases with a positive result (>0) were classified as progression and those with a negative result (<0) as regression; ±0 was defined as no change.

Changes in minimal stenosis diameter correlated well with changes in relative diameter reduction ($r = 0.74$; $p < 0.001$). The incidence of regression or progression/no change was identical if classification of patients was based on changes in minimal stenosis diameter instead of relative diameter reduction.

Progression from subtotal to total occlusion (99% to 100%) and recanalization of previously occluded coronary arteries were not classified as progression or regression, respectively, because mechanisms not related to the atherosclerotic process may be operative in these cases (12).

Thallium-201 scintigraphy. Beta-adrenergic blocking agents and antianginal medications were discontinued 48 h before the test. After an overnight fasting period, symptom-limited electrocardiographic (ECG) exercise testing was performed on a bicycle ergometer. The ECG tracings and blood pressure readings were obtained every minute. Exercise was terminated when patients experienced progressive anginal chest pain or physical exhaustion or when 3-mm horizontal ST segment depression was reached. Maximal heart rate-pressure product 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 (MVO_2) over a wide range of exercise levels (13).

One minute before termination of the exercise test, 2 mCi of thallium-201 was injected intravenously and exercise was 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 pinhole collimator. Rest images were acquired after a rest period of 4 h in the identical projection.

Thallium-201 scintigrams were analyzed by a technician who did not know the patient's identity. Left ventricular cross sections perpendicular to the long axis were reconstructed from the raw data. To define areas with decreased thallium-201 uptake, all reconstructed myocardial cross sections were analyzed by a semiquantitative program. In brief, after the geometric center of each cross section is defined, 60 radii are projected outward from this point at equal angular spacing. A search is made along each radius for the peak count rate, which is then normalized to the maximal count rate in each patient. The results are displayed as a circumferential plot over 360°. Abnormal myocardial sections are identified by comparing each circumferential plot to the lower limit of normal as defined by the counts in 15 patients free of cardiac abnormalities who were analyzed correspondingly. If a section showed decreased thallium-201 uptake, no attempt was made to grade the degree of abnormality. The mean of all cross sections was calculated and expressed in degrees of left ventricular circumference. Intraobserver variability was ±5% and interobserver variability ±9%. This method was validated by comparing perfusion defects with histopathologic findings in patients who died during the course of acute myocardial infarction (14).

JACC Vol. 19, No. 1
January 1992 34–42

Myocardial perfusion and ischemia. Severity of myocardial ischemia is determined by the deficit between stress-induced myocardial oxygen consumption and coronary vascular capability. The area of a reversible thallium-201 perfusion defect has to be judged against the level of myocardial oxygen consumption during which it was recorded. To correlate the size of the reversible thallium-201 perfusion defect (ischemia) to the corresponding rate-pressure product, the following index was calculated:

$$\text{Perfusion} = \frac{\text{Ischemia}}{\text{Rate-pressure product}}.$$

Changes in myocardial perfusion during the observation period were expressed by $\text{Delta}_{\text{perfusion}}$:

$$\text{Delta}_{\text{perfusion}} = \frac{\text{Ischemia}_{\text{Begin}}}{\text{Rate-pressure product}_{\text{Begin}}} - \frac{\text{Ischemia}_{\text{End}}}{\text{Rate-pressure product}_{\text{End}}}.$$

Whenever myocardial perfusion relative to myocardial oxygen consumption improved, by either a reduction in ischemia or an increase in rate-pressure product, the difference became positive. In patients in whom myocardial perfusion deteriorated, by either an increase in ischemia or a reduction in rate-pressure product, the index became negative.

Metabolic variables. After an overnight fasting period, body weight was obtained and blood drawn for measurement of serum lipids and lipoproteins (total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol as well as triglycerides).

Intervention program. Patients assigned to the intervention group stayed on a metabolic ward during the initial 3 weeks of the program, where they were instructed how to lower the fat content of their regular diet (8). The guidelines they received were based on the American Heart Association recommendations (15), which call for a low fat, low cholesterol diet (protein 15%, carbohydrates 65%, fat <20 energy%, cholesterol <200 mg/day, polyunsaturated/saturated fatty acids ratio >1).

Patients were asked to exercise daily at home on a bicycle ergometer for a minimum of 30 min close to their target heart rate, which was determined as 75% of the maximal heart rate during symptom-limited exercise. During this phase, patients were receiving their regular antianginal medication including beta-blocking agents. In addition, they were expected to participate in at least two group training sessions of 60 min each week. Combined compliance for home and group exercise was 60%; exceeding weekly requirements was not honored by a score of >100%; compliance ranged between 21% and 92%.

Antianginal medications including nitrates, beta-blockers and calcium channel blockers were prescribed as needed. Lipid-lowering drugs were not part of the regimen.

Informative sessions were conducted at regular intervals four 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 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 I) (15). However, adherence to these guidelines was left to their own initiative and "usual care" was rendered by their private physician. 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. Differences between both groups with respect to coronary morphology were examined by chi-square analysis and with respect to heart rate, blood pressure and physical work capacity by analysis of variance. To test sequential metabolic data for statistical significance, a simple variable was calculated for each patient. Because body weight remained stable after 3 months, measurements obtained at 6, 9 and 12 months reflect effects of treatment. These values were averaged and used for statistical analysis (8).

Results

Study group (Table 1). A total of 38 patients were recruited for the study. After exclusion of one matched pair, angiograms were available from 36 patients for final evaluation (18 patients in each group). Their mean age was 51 ± 6 years; 25 patients (69%) had previously had an acute myocardial infarction. During the observation period, two additional patients in the control group sustained a nonfatal myocardial infarction (Patients 24 and 31); subsequently, Patient 24 underwent aortocoronary bypass grafting for postinfarction angina. Results obtained in this patient were excluded from further analysis of stress testing and metabolic changes; angiographic data, however, were included.

Before entering the study, patients had smoked an average of 22 pack-years of cigarettes. There were only five nonsmokers among all patients recruited for the study (two in the control group and three in the intervention group). After recruitment, all but three patients in the control group indicated that they had stopped smoking.

One patient from the intervention group refused to undergo final evaluation and repeat coronary angiography at 1 year; therefore, he and his matched control patient were excluded. His physical work capacity had improved significantly during the study period and he was asymptomatic during daily life.

Physical work capacity: hemodynamic variables. In the intervention group, systolic blood pressure at rest decreased significantly from 119 ± 16 to 109 ± 11 mm Hg ($p < 0.05$), diastolic blood pressure tended to decrease (85 ± 1 vs. 81 ±

Table 1. Change in Coronary Morphology, Stress-Induced Ischemia and Total Cholesterol

Pt No.	Coronary Morphology	$Delta_{perfusion}$	Cholesterol (mg/dl) Baseline	Cholesterol (mg/dl) Average
Intervention group (n = 18)				
1	Regression	4.29	248	170
2	Progression	1.92	226	157
3	No change	0.13	252	209
4	Progression	0.36	239	236
5	Regression	1.43	208	177
6	Progression	4.59	187	170
7	Regression	0.36	232	214
8	No change	0	257	148
9	Progression (subtotal to total occl)	0.11	299	240
10	Regression	0.24	179	156
11	Regression	1.63	237	209
12	No change	0.06	224	214
13	Progression (new occl)	1.73	250	202
14	No change	−0.03	271	239
15	Regression	0	283	221
16	Regression	1.23	224	192
17	No change (recanal; new lesion)	0.80	281	210
18	No change	0.16	261	178
Total	Regression (N = 7) No change (n = 6) Progression (n = 5)			
Mean ± SD		1.05 ± 1.4*	242 ± 32	198 ± 27†
Control group (n = 18)				
19	No change	0.47	224	224
20	No change (subtotal to total occl)	4.27	243	218
21	No change	−0.53	242	214
22	Progression	+4.31	264	289
23	No change	0.15	240	271
24	Progression (AMI, CABG)	—	—	—
25	No change	1.18	263	249
26	Progression (subtotal to total)	0.09	240	250
27	Progression (subtotal to total occl; new lesion)	1.13	281	287
28	No change	−0.30	221	242
29	No change	−0.83	197	229
30	Regression	0	223	236
31	Progression (new occl, AMI)	3.49	243	360
32	No change	−0.48	179	203
33	No change	1.11	238	184
34	Progression (new lesion)	1.03	306	277
35	No change	−0.05	259	252
36	No change	−1.30	265	241
Total	Regression (n = 1) No change (n = 11) Progression (n = 6)			
Mean ± SD		−0.09 ± 1.88	243 ± 30	239 ± 80

*Significantly different from control ($p < 0.05$); †significantly different from control ($p < 0.002$). AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; cholesterol average and cholesterol level during the observation period and at baseline, respectively; $Delta_{perfusion}$ (see description in Methods); occl = occlusion; Pt = patient; recanal = recanalization.

7 mm Hg: p = NS), physical work capacity improved from 161 ± 34 to 194 ± 42 W ($p < 0.01$), maximal heart rate increased from 149 ± 25 to 157 ± 22 beats/min ($p < 0.05$) and maximal rate-pressure product increased from 25 ± 6.3 × 10^3 to 27.2 ± 5.3 × 10^3 ($p < 0.01$).

In the control group, systolic blood pressure at rest also decreased significantly from 129 ± 21 to 120 ± 15 mm Hg ($p < 0.05$), whereas diastolic blood pressure at rest remained unchanged (85 ± 12 vs. 86 ± 7 mm Hg: p = NS). Physical work capacity (153 ± 42 vs. 154 ± 40 W), maximal heart rate

JACC Vol. 19, No. 1
January 1992:34–42

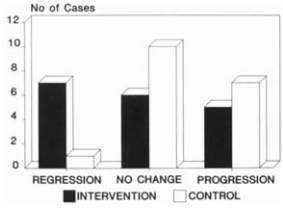

Figure 1. Regression of coronary lesions was observed in seven patients in the intervention group compared with one patient in the control group. No change or progression was detected in 11 patients in the intervention group and 17 patients in the control group. There was a significant difference between groups ($p < 0.048$).

(131 ± 18 vs. 134 ± 20 beats/min) and maximal rate-pressure product (24.1 ± 5.2 × 10^3 vs. 23.1 ± 6.1 × 10^3) also remained essentially unchanged.

At 12 months, a statistical relevant difference was detected between both groups with respect to physical work capacity ($p < 0.001$), maximal rate-pressure product ($p < 0.05$), rest heart rate ($p < 0.02$) and maximal systolic blood pressure ($p < 0.02$).

Changes in coronary morphology (Table 1, Fig. 1 to 3). A total of 105 stenoses were evaluated by digital image processing (mean 2.9 stenoses/patient). Progression was noted in 11 patients (intervention n = 5, control n = 6), no change was seen in 17 patients (intervention n = 6, control n = 11) and regression occurred in 8 patients (intervention n = 7, control n = 1). Overall changes in coronary morphology (that is, progression, no change or regression) differed significantly between both groups ($p < 0.048$). The grading system employed was relatively insensitive to the detection of new lesions because it required a change of >10% before it was classified as significant. Therefore, only three new lesions were observed (intervention n = 1, control n = 2). In four patients, a subtotally occluded vessel (lumen diameter reduction 99%) progressed to total occlusion (intervention n = 1, control n = 3); two vessels with less than critical diameter reduction (<75%) progressed to total occlusion (intervention n = 1, control n = 1). In four patients (11%), simultaneous progression and regression of coronary lesions was noted.

Change in myocardial perfusion (Table 1, Fig. 2 and 4). In the intervention group, myocardial perfusion during maximal physical stress expressed as $delta_{perfusion}$ improved in 14 patients and remained unchanged or deteriorated slightly in 4 patients. In the control group, perfusion deteriorated in eight patients; it improved or remained unchanged in nine patients and one patient was excluded after coronary bypass surgery. The average change was +1.05 ± 1.4 in the intervention group versus −0.09 ± 1.88 in the control group ($p < 0.05$).

Myocardial perfusion, maximal rate-pressure product and physical work capacity according to change in coronary morphology (Table 1, Fig. 2 and 4). To compare patients with progression or no change in coronary morphology with patients with regression, both groups were combined. In patients with regression, a significantly greater increase in physical work capacity was observed compared with patients with no change or progression (regression +47 ± 34 W; no change/progression +9 ± 26 W; $p < 0.001$). No significant difference was detected with respect to change in maximal rate-pressure product (progression or no change 0.3 ± 4.3; regression 1.5 ± 2.73; p = NS) or myocardial perfusion (progression or no change 0.31 ± 1.7; regression 1.15 ± 1.43; p = NS). There was only a weak correlation between change in physical work capacity and change in rate-pressure product ($r = 0.37$; p = NS). In individual patients, there was a striking dissociation between improvement in myocardial perfusion and progression of coronary artery disease (Patients 2, 6, 13, 27 and 34).

Metabolic variables (Tables 1 and 2, Fig. 5). The results of metabolic evaluation in this group of patients were discussed in detail in a previous publication (8). According to 24-h diet protocols in the intervention group, there was a significant lowering of energy intake from 2,298 ± 697 to 1,602 ± 758 kcal/day ($p < 0.003$), fat consumption from 111.7 ± 44.4 to 52 ± 23.9 g/day ($p < 0.0004$), saturated fatty acids from 42.5 ± 20.4 to 14.3 ± 8.1 g/day ($p < 0.0001$) and dietary cholesterol from 402.8 ± 186.1 to 161.3 ± 100.3 mg/day ($p < 0.0001$). Intake of polyunsaturated fatty acids remained unchanged (14.9 ± 9.8 vs. 9 ± 6.3 g/day, p = NS). As indicated by the large standard deviations, compliance varied considerably among individual patients. In the control group, none of these variables changed significantly throughout the observation period.

Each group was subdivided according to changes in coronary morphology; at baseline all subgroups were comparable with respect to total cholesterol level. During follow-up, the lowest levels were observed in the intervention group showing regression of coronary lesions and the highest in the control group with lesion progression. Cholesterol levels observed in the intervention group with progression were unexpectedly low (201 ± 38 mg/dl).

Discussion

The message conveyed by the results of this study is twofold. First, beneficial effects on the natural course of coronary atherosclerosis are not confined to aggressive programs, which generally find acceptance only by a small minority of motivated patients. Second, patients participating in regular physical exercise may achieve improvement in myocardial perfusion independently from regressive changes in coronary lesions.

Patient selection and compliance. Patients participating in this study were recruited after undergoing routine coronary

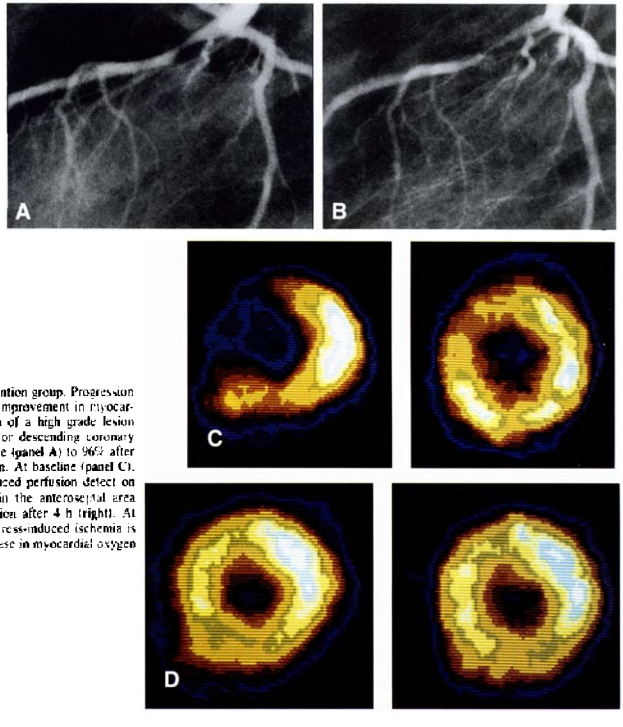

Figure 2. Patient 9. Intervention group. Progression of coronary lesion versus improvement in myocardial perfusion. Progression of a high grade lesion in the proximal left anterior descending coronary artery from 77% at baseline (panel A) to 96% after 12 months (panel B) is seen. At baseline (panel C), there is a large stress-induced perfusion defect on thallium-201 scintigraphy in the anteroseptal area (left) with total redistribution after 4 h (right). At 12 months (panel D), no stress-induced ischemia is detectable despite an increase in myocardial oxygen consumption.

angiography for stable angina pectoris. Apart from medical considerations, only willingness to participate for 12 months was a prerequisite for inclusion in the study; nearly all patients were fully employed and had to follow a regular working schedule with limited spare time for exercise sessions. After recruitment, only one patient dropped out (because of refusal of repeat angiography). The dietary schedule the patients were asked to follow was based on American Heart Association recommendations (phase 3) (15). Adherence to these recommendations was frequently encouraged by educational sessions and checked by dietary protocols, which regularly yielded a satisfactory compliance rate (16). However, objective measurements of serum lipoproteins indicated that actual behavior was less than ideal. Particularly, after the 1st 6 months, there seemed to be an erosion of dietary discipline (8). Average changes in serum lipoproteins in the intervention group were −18% for cholesterol, +6% for high density lipoprotein, −12% for low density lipoprotein, and −23% for triglycerides. The following changes were achieved in the Cholesterol-Lowering Atherosclerosis Study (CLAS) (5) (cholesterol −26%, high density lipoprotein +37%, low density lipoprotein −43% and triglycerides −22%) and the Life-Style Heart Trial (6) (cholesterol −24%, high density lipoprotein −3%, low density lipoprotein −37% and triglycerides +22% (Table 3).

Group training sessions proved to be an instrument paramount to maintaining a high level of physical activity, whereas home training was pursued less vigorously. As judged by the compliance rate of 60%, patients exercised for an average of >3 h/week at a moderate to high activity level, a level that has been shown to be associated with a protective effect in primary prevention studies (17).

JACC Vol. 19, No. 1
January 1992:34–42

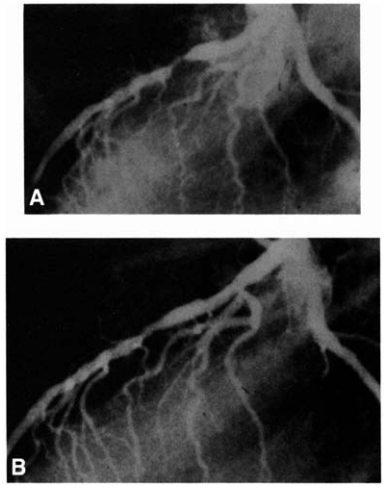

Figure 3. Patient 1. Intervention group. Regression of coronary lesion. Regression of a high grade proximal lesion in the left anterior descending coronary artery from 79% at baseline (**panel** A) to 54% at 12 months (**panel** B) is seen.

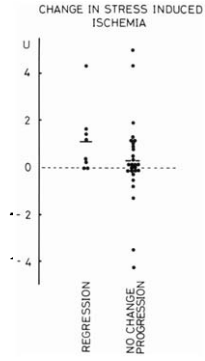

Figure 4. Change in stress-induced myocardial ischemia according to coronary morphology. In patients with regression of coronary lesions, there was a significant reduction in stress-induced myocardial ischemia. Patients with no change or progression did not differ significantly from patients with regression. Myocardial perfusion improved markedly in individual patients despite unchanged or worsened coronary morphology.

Changes in coronary morphology. Coronary atheromatosis progressed at a significantly slower pace in patients participating in the intervention group compared with the control group. Although regression of coronary stenoses was noted in seven patients (39%), this beneficial effect was nearly offset by progression in five patients (28%); coronary morphology remained unchanged in six patients (33%). Therefore, no significant net regression was achieved in the group as a whole. In the control group, definite progression of coronary artery disease was detected in six patients (33%). Because coronary lesions remained unchanged in 11 patients (61%) and regression was noted in only 1 patient (6%), there was obvious deterioration of coronary morphology. The rate of progression observed in this particular group of patients corresponds to the natural course of coronary artery disease defined by previous studies (18–21). New lesions were detected with a frequency of 8%, which is higher than the rate reported by Frick et al. (21). No significant difference with respect to new coronary closures was observed between groups.

Initially, all subgroups were comparable with respect to the total cholesterol level. During follow-up, the lowest levels were observed in patients with regression of coronary lesions, whereas levels >270 mg/dl invariably resulted in detectable progression of lesions within 1 year (Patients 22, 27, 31 and 34). It is of interest to note, however, that even excellent adherence to the dietary schedule did not invariably result in regression of coronary lesions (Patients 2, 6 and 8). Conversely, regression was noted even in patients with only moderate compliance (Patients 7, 15 and 30). Therefore, no clear dose-response relation could be established between directional change in coronary lesions and adherence to the intervention program; optimal control of metabolic variables did not guarantee improvement of coronary status. Scrutiny of other risk factors such as smoking and blood pressure control did not yield a valid explanation.

Taking the inherent differences in angiographic evalua-

Table 2. Cholesterol Levels According to Change in Coronary Morphology

	Baseline (mg/dl)	Average (mg/dl)	Change (%)
Intervention group			
Regression (n = 7)	230 ± 32	191 ± 25*	−17
No change (n = 6)	258 ± 20	201 ± 31*	−22
Progression (n = 5)	240 ± 41	201 ± 38*	−16
Control group			
Regression (n = 1)	—	—	—
No change (n = 11)	234 ± 27	229 ± 25	−3
Progression (n = 5)	267 ± 28	292 ± 41*	+10

*Significantly different from baseline ($p < 0.05$). Baseline and average = baseline and average cholesterol level during observation period.

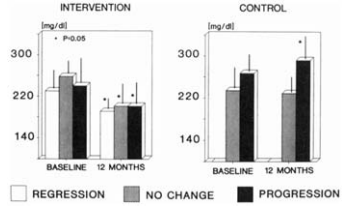

Figure 5. Metabolic variables according to change in coronary morphology. Total cholesterol, cholesterol/high density lipoproteins and triglycerides were lower in patients with regression of coronary lesions. However, a significant difference was observed only for total cholesterol.

tion into account, these results are compatible with those obtained in CLAS (5). The rate of regression observed in the Life-Style Change Study (6), however, is more than twice the rate noted in our study and five times the rate detected in CLAS (5); coronary lesions remained unchanged in only one patient.

Physical work capacity and stress-induced ischemia versus coronary status. With only few exceptions, all patients participating in the intervention study experienced not only significant improvement in physical work capacity as a result of peripheral adaptation, but also a reduction in stress-induced ischemia (thallium-201 scintigraphy) in the setting of increased myocardial oxygen consumption (maximal rate-pressure product). These changes suggest improvement in myocardial perfusion during maximal exercise, a finding supported by several other studies (22,23). A surprising finding of this study was the dissociation between directional changes in stress-induced myocardial ischemia and coronary morphology. A decrease in myocardial ischemia was not limited to patients with a reduction in coronary lesions, but also occurred in those with significant progression (Patients 2, 6, 13, 27 and 34). Therefore, alternative mechanisms are likely to contribute to improvement in coronary flow.

Regular physical exercise has been shown to favorably affect whole blood rheology and thereby possibly benefit peripheral and myocardial perfusion (24,25). Recruitment and development of preformed collateral vessels may represent a second alternative mechanism. Experimental work in dogs (26) has demonstrated improvement in coronary vascular capacity in response to physical conditioning; angiographic studies in humans (27), however, have failed to substantiate this hypothesis. Because coronary angiography is unable to detect the majority of intramural collateral vessels with a diameter < 100 μm, this negative finding is not a surprise (28). Moreover, because collateral channels are unlikely to carry substantial flow during rest, it may be necessary to obtain measurements during physical stress. Different diagnostic techniques with a higher resolution are needed to settle this issue in humans.

A highly significant relation was detected between improvement in exercise capacity and changes in coronary morphology. Patients with regression gained 29% in external work delivery compared with 6% in patients with no change or progression ($p < 0.001$). Because only a weak relation was detected between physical work capacity and maximal rate-pressure product ($r = 0.37$; p = NS), peripheral adaptation seems to represent the underlying mechanism. Therefore, in this particular group of patients, improvement in physical fitness seemed to contribute to regression of coronary lesions.

Limitations of the study. This study is unable to clearly identify the mechanism responsible for the discrepancy between change in coronary lesions and reduction in stress-induced myocardial ischemia in several patients. To date, only limited evidence has been gathered in a different group of patients undergoing a similar study protocol. Although significant improvement in whole blood viscosity could be documented in these patients, the physiologic relevance to myocardial perfusion remains to be demonstrated.

Clinical implications. Patients willing to devote their time and effort to intensive physical exercise and a low fat diet may experience benefit from this form of therapy in two respects. First, progression of coronary artery disease may be slowed in a considerable number of patients; some may even achieve regression of coronary lesions. However, there is no guarantee to achieve this goal invariably, even in the most active and compliant patient. Conversely, favorable effects occur in patients with no more than average ambition toward following the stipulations of the protocol. Second, regression of coronary lesions does not seem to constitute an essential and indispensable precondition for improving stress-induced myocardial ischemia. Different compensatory mechanisms may be activated in some patients by intensive physical exercise.

Table 3. Comparison of Angiographic Results With Data From Recently Published Studies

Study (ref. no.)	Regression (%)	No Change (%)	Progression (%)
Present study			
Rx (n = 18)	39	33	28
Ctrl (n = 18)	6	61	33
CLAS (5)*			
Rx (n = 80)	16.2	45	38.8
Ctrl (n = 82)	2.4	39.6	61
Life-style (6)			
Rx (n = 22)	82	0	18
Ctrl (n = 19)	42	5	53
Brown et al. (7)			
L/C (n = 38)	32	47	21
N/C (n = 36)	39	36	25
Ctrl (n = 46)	11	43	46

*Native vessels only. CLAS = Cholesterol-Lowering Atherosclerosis Study; Ctrl = control; L/C = lovastatin/cholestipol; N/C = niacin/colestipol; ref. = reference; Rx = treatment.

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