Various Intensities of Leisure Time Physical Activity in Patients With
Coronary Artery Disease: Effects on Cardiorespiratory Fitness and
Progression of Coronary Atherosclerotic Lesions

RAINER HAMBRECHT, MD, JOSEF NIEBAUER, MD, CHRISTIAN MARBURGER, MD,
MARTIN GRUNZE, MD, BARBARA KÄLBERER, RN, KLAUS HAUER,
GÜNTHER SCHLIERF, MD, WOLFGANG KÜBLER, MD, FACC, GERHARD SCHULER, MD
Heidelberg, Germany

Objectives. This study was designed to define the effect of
different levels of leisure time physical activity on cardiorespira-
tory fitness and progression of coronary atherosclerotic lesions in
unselected patients with coronary artery disease.

Background. It has been shown in various studies that regres-
sion of coronary atherosclerotic lesions can be achieved by means
of lipid-lowering drugs, reduction of fat consumption and physical
exercise.

Methods. Patients were prospectively randomized either to
an intervention group (n = 29) participating in regular physical
exercise or to a control group (n = 33) receiving usual care.
Energy expenditure in leisure time physical activity was estimated
from standardized questionnaires and from participation in group
exercise sessions. After 12 months of participation, repeat coro.
nary angiography was performed; coronary lesions were mea-
sured by digital image processing.

Results. After 1 year, patients in the intervention group
achieved an increase in oxygen uptake at a ventilatory threshold of
7% (p < 0.001) and peak exercise of 14% (p < 0.05), whereas a
significant decrease was observed in patients in the control group.
To achieve significant improvement in cardiorespiratory fitness,
-1,400 kcal/week had to be expended in the form of leisure time
physical activity (p < 0.001). The mean energy expended in such
activity was 1,876 ± 163 kcal/week in the intervention group and
1,187 ± 97 kcal/week in the control group (p < 0.001). In the
intervention group, regression of coronary artery disease was
noted in 8 patients (28%), progression of disease in 3 (10%) and
no change in coronary morphology in 18 (62%). In contrast,
coronary artery disease progressed at a significantly faster rate in
patients in the control group (progression in 45%, no change in
49% and regression in 6%) (p < 0.001 vs. intervention). When the
two groups were combined, the lowest level of leisure time
physical activity was noted in patients with progression of disease
(1,022 ± 142 kcal/week) as opposed to patients with no change
(1,533 ± 122 kcal/week) or regression of disease (2,204 ±
237 kcal/week) (p < 0.005).

Conclusions. Measurable improvement in cardiorespiratory
fitness requires ~1,400 kcal/week of leisure time physical activity;
higher work loads are necessary to halt progression of coronary
atherosclerotic lesions (1,533 ± 122 kcal/week), whereas regress-
ion of coronary lesions is observed only in patients expending an
average of 2,200 kcal/week in leisure time physical activity,
amounting to ~5 to 6 h/week of regular physical exercise.

(J Am Coll Cardiol 1993;22:468-7)

Primary prevention studies have identified the protective
effect of regular physical exercise in patients with coronary
artery disease (1-3). In addition to its beneficial effect on
coronary risk factors, regular physical exercise increases the
efficiency of oxygen extraction in peripheral skeletal muscles
and reduces stress-induced myocardial ischemia in patients
with stable coronary artery disease (4-8); however, no

clear-cut guidelines with regard to training intensity neces-
sary to achieve these advantageous training effects have yet

been defined. This study was designed to determine the level
of physical activity required to improve cardiorespiratory
fitness and to retard progression of coronary atherosclerotic
lesions.

Methods

Patient selection. Patients participating in this study were
recruited after routine coronary angiography for angina
pectoris. Inclusion criteria were male gender, stable angina
pectoris, willingness to participate in the study for at least 12
months and permanent residence within 25 km of the training
facilities at Heidelberg. Patients with left main coronary
artery disease, previous coronary angioplasty or coronary
bypass surgery, severely depressed left ventricular ejection
fraction (<35%), significant valvular heart disease, rhythm
disturbances (Lown grade IVb), uncontrolled hypertension,
The ventilatory threshold was evaluated in this way by progressive anginal chest pain or severe dyspnea or when 3-mm horizontal ST segment depression was reached. The maximal rate-pressure product was calculated from maximal, simultaneously recorded heart rate and systolic blood pressure during exercise (11).

Respiratory gas exchange variables. Respiratory gas exchange data were determined continuously throughout the exercise test using a commercially available system (Jaeger EOS-Sprint). The ventilatory threshold was defined as the oxygen uptake (V\text{O}_2) before the systematic increase in the ventilatory equivalent for oxygen without a concomitant increase in the ventilatory equivalent for carbon dioxide (12). The ventilatory threshold was evaluated in this way by two independent observers who were unaware of the patient's identity or the sequence of the exercise test performed.

Cardiac catheterization. Cardiac catheterization was performed by the percutaneous femoral approach; left ventriculography in two orthogonal projections was followed by coronary angiography according to the Judkins technique. A minimum of six standard projections were 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, calcium channel blocking agents) were used during either catheterization.

Digital image processing. Evaluation of coronary angiograms was performed by two technicians who were unaware of the sequence of films, the patient's identity or group assignment. Films were viewed in pairs using 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 digitalization, were transferred to the image processing system (Kontron Mipron), where they were stored in a 512 x 512 matrix. Because all images were obtained in the 6-in. (15 cm) angiographic mode, pincushion distortion is minimal (13), and correction is 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 (14). Minimal stenosis diameter was measured, and percent diameter reduction was calculated by comparing the minimal stenosis diameter with the adjacent normal segment. No attempt was made to calculate longitudinal dimension of lesions or atherosclerotic mass because these variables have demonstrated considerable variability (13,15). Owing to 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 this method, 25 stenoses were analyzed three times on different days by three technicians. The standard deviation (SD) between repeated measurements of percent diameter reduction was 4.4%. Consequently, only changes between sequential measurements >10% (2 SD) were considered relevant. Stenoses with <10% change in diameter reduction were classified as unchanged (grade ±0). A positive difference of >10% between baseline and final measurement was graded as progression (grade +1) and a negative difference of >10% as regression (grade −1).

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 mm ± 2.9 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 of disease. Changes in minimal stenosis diameter correlated well with changes of relative diameter reduction (r = 0.81, p < 0.001). If classification of patients had been based on changes in minimal stenosis diameter instead of relative diameter reduction, the incidence of regression, progression or no change would have been identical.

Progression from subtotal occlusion to total occlusion (i.e., from 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 (16).

In patients with multiple stenoses the fate of each individual lesion probably cannot be considered statistically independent, and therefore each patient has to be treated as a statistical unit. Moreover, in rare instances progression and regression of disease 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 reduc-
tion or minimal diameter. Cases with a positive sum of grades (>0) were classified as progression, those with a negative result (<0) as regression, and ±0 was defined as no change. Differences between both groups were also evaluated on a per lesion basis (see later, Table 6).

**Metabolic variables.** After an overnight fasting period, body weight was measured, and blood was drawn for measurement of serum lipids and lipoproteins. Total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were measured at baseline, at hospital discharge and quarterly (4–6,17).

Assessment of leisure time physical activities. Energy expenditure in leisure time physical activity was estimated using a modified Minnesota leisure time physical activity questionnaire (18,19). The metabolic cost of a specific activity was estimated as the product of the intensity score and the duration of exercise in minutes per day. Intensity scores are based on experiments in which rates of VO$_2$ were measured while subjects performed various specific activities (20). Patients were interviewed at least twice during the treatment period by the same technician. Activities recorded were those performed during the previous weekend and on the previous 2 days. From each interview, energy expended per week (in kilocalories per week) in leisure time physical activity was calculated. In addition, attendance for group exercise sessions was recorded regularly. Energy expenditure per week, obtained from group training, was added to calculated energy expenditure data obtained from questionnaires, which did not include supervised training sessions. For further analysis the mean value of energy expenditure in all leisure time physical activities per week over the 1-year period was used.

**Intervention group.** Patients assigned to the intervention program stayed on a metabolic ward for the initial 3 weeks of the intervention program to adjust to a low fat diet. The guidelines they received were based on the American Heart Association recommendation, phase III (21); it called for a low fat, low cholesterol diet (protein 15%, carbohydrates 65%, fat <20 energy%, cholesterol <200 mg, polyunsaturated/saturated fatty acids ratio >1).

Initial training sessions were conducted individually under close supervision on the metabolic ward for the 1st 3 weeks. Patients exercised six times daily for 10 min on a cycle ergometer. Work loads were adjusted so that 75% of the symptom-limited maximal oxygen uptake (VO$_{2\text{max}}$) was reached. On hospital discharge, patients were given, on loan, a cycle ergometer and were asked to exercise daily for a minimum of 30 min at a rate close to their target heart rate, which was determined as 75% of the VO$_{2\text{max}}$ during symptom-limited exercise. In addition they were expected to participate in at least two group training sessions of 60 min/week. Each session consisted of jogging, calisthenics and ball games.

Aspirin and antianginal medications, including nitrates, beta-blockers and calcium channel blockers, were prescribed as indicated; lipid-lowering drugs were not part of the regimen. Patients were seen at 3-month intervals for assessment of metabolic variables and stress testing.

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 ways of lowering fat consumption. On hospital discharge, patients were seen at 3-month intervals for stress testing and metabolic assessment. Patients were given usual care by the private physician, who also prescribed antianginal medications; however, patients were asked not to take lipid-lowering drugs.

**Statistical analysis.** For statistical evaluation, nonparametric tests (Mann-Whitney U test and Wilcoxon signed-rank and chi-square tests) were used. To examine sequential metabolic data for statistical significance, all measurements obtained after initiation of therapy (i.e., 3, 6, 9, and 12 months) were averaged and compared with baseline values. A multivariate statistical model was built in steps using logistic regression analysis for evaluating the independent influence of mean change in metabolic variables (average minus baseline), mean kilocalories expended weekly in physical activities, group assignment, smoking behavior and age on changes in coronary morphology, expressed as a trichotomous variable (regression, no change, progression) (22). The variable least strongly correlated with changes in coronary morphology was eliminated first (backward elimination procedure); subsequent variables were eliminated if they added no more predictive information. Elimination ended when all of the remaining variables added significantly to the sum of $r^2$.

**Results**

Clinical characteristics (Table 1). In all patients included in this analysis, complete cardiorespiratory data were available at baseline. They were recruited as part of a larger study, primarily concerned with regression of coronary lesions (5). Of 88 patients who had met the inclusion criteria, 45 were randomized to the intervention group and 43 to the control group. Patients in the control group did not differ significantly from those in the intervention group with respect to age, number of obstructed vessels, severity of coronary artery disease (Gensini score) (23), left ventricular ejection fraction (LVEF), and other variables.

**Table 1. Clinical Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group</th>
<th>Control Group</th>
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</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>53 ± 6</td>
<td>54 ± 7</td>
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<tr>
<td>Previous AMI</td>
<td>20 (60)</td>
<td>26 (79)</td>
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<tr>
<td>LVEF (%)</td>
<td>58 ± 9</td>
<td>55 ± 8</td>
</tr>
<tr>
<td>Gensini score</td>
<td>32 ± 16</td>
<td>30 ± 19</td>
</tr>
<tr>
<td>Vessels involved</td>
<td>3.1 ± 1.5</td>
<td>3.0 ± 1.6</td>
</tr>
</tbody>
</table>

Values presented are mean value ± SD or number (%) of patients. AMI = acute myocardial infarction; LVEF = left ventricular ejection fraction.
ejection fraction or history of previous myocardial infarction.

Dropouts, clinical events. Before initial stress testing, five patients (four from the intervention group, one from the control group) withdrew their consent for various nonmedical reasons, and one patient from the intervention group was scheduled for bypass surgery by his private physician. Three patients from the intervention group were excluded from further participation because nonsustained ventricular tachycardia was detected by Holter ambulatory electrocardiographic (ECG) monitoring during the first training session. One patient from the control group was excluded after 1 week of participation for alcoholism. In the intervention group, four dropouts and one patient who developed orthopedic problems because of an accident could not repeat stress testing after 1 year. There were two cardiac arrests in the intervention group: One patient experienced ventricular tachycardia after exceeding his training heart rate during group exercise by >30%, as documented by Holter monitoring he was resuscitated by DC countershock. The second was found in the street with no vital signs. One patient from the control group experienced cardiac arrest in the course of an acute myocardial infarction. Furthermore, coronary angioplasty was necessary in one patient from the control group because of acute myocardial infarction and in another control patient because of unstable angina pectoris. Repeat 1-year testing was therefore performed in 29 of 45 patients from the intervention group and in 33 of 43 control subjects.

Medical treatment (Table 2). Initially, 83% of patients recruited for the intervention group were receiving beta-blockers, 52% calcium channel blockers, 76% nitrates and 17% angiotensin-converting enzyme inhibitors. The corresponding numbers for patients in the control group were 82%, 52%, 79% and 3%. No significant change in dosages was noted in either the intervention or the control group after 12 months, but there was a tendency to lower dosages for all four drugs in the intervention group. No patient was receiving lipid-lowering drugs.

Energy expenditure in leisure time physical activity (Fig. 1 to 3). The mean attendance at the training sessions was 62 ± 24%, and compliance with home training was calculated at 60%, amounting to a total of 3.3 h/week leisure time physical activity. The mean weekly energy expenditure in leisure time physical activity (±SEE) was 1,876 ± 163 kcal/week (range 466 to 3,536) in the intervention group and 1,187 ± 97 (range 0 to 2,250) in the control group (p < 0.001). Each group was further classified according to changes in coronary morphology. Patients with progression of disease

**Table 2. Medical Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
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<th>With Dosage Decrease</th>
<th>With Dosage Unchanged</th>
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<td>24</td>
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<td>11</td>
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<tr>
<td>Control</td>
<td>27</td>
<td>9</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Nitrates</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intervention</td>
<td>22</td>
<td>1</td>
<td>9</td>
<td>13</td>
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<tr>
<td>Control</td>
<td>26</td>
<td>4</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Calcium blockers</td>
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</tr>
<tr>
<td>Intervention</td>
<td>15</td>
<td>2</td>
<td>7</td>
<td>7</td>
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<tr>
<td>Control</td>
<td>17</td>
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<tr>
<td>Intervention</td>
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<td>1</td>
</tr>
<tr>
<td>Control</td>
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<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Diuretic agent</td>
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</tr>
<tr>
<td>Intervention</td>
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<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*No significant changes in dosages were noted in either the intervention or the control group.
Figure 2. Absolute change in minimal stenosis diameter (MSD) is plotted against the energy expenditure in leisure time physical activity (LTPA). There was a weak but significant correlation between both variables.

Figure 3. Patient 48, intervention group. Regression of coronary lesion after 12 months of intervention with regular physical exercise (mean energy expenditure in leisure time physical activity 2,220 kcal/week) and a low fat diet. Regression of a lesion in the proximal left descending coronary artery (45° left anterior oblique projection) from 70% at baseline (left) to 59% after 12 months (right).

showed the lowest levels of energy expenditure irrespective of group assignment (intervention group 1,059 ± 461 kcal/week; control group 1,014 ± 153 kcal/week). Energy expenditure was higher in patients with no change (intervention group 1,758 ± 190 kcal/week; control group 1,279 ± 121 kcal/week) and highest in patients with regression (intervention group 2,445 ± 275 kcal/week; control group 1,735 ± 134 kcal/week). The difference between the control and intervention groups did not reach statistical significance. Within the intervention group there was a significant difference in energy expenditure among the subgroups of progression, no change and regression (p < 0.05). No significant difference was detected among subgroups within the control group (p = 0.19). For further calculations both groups were combined. The lowest activity level was noted in patients with progression (1,022 ± 142 kcal/week) compared with patients with no change (1,533 ± 122 kcal/week) or regression (2,204 ± 237 kcal/week) (p < 0.005). There was a weak but significant correlation between energy expenditure in leisure time physical activity and change in minimal stenosis diameter (r = 0.45, p < 0.01).

Metabolic variables (Table 3). In the intervention group, body mass index (body weight) decreased by 5% (p < 0.001), total cholesterol by 10% (p < 0.001), LDL by 8% (p < 0.001) and triglycerides by 21% (p < 0.001); HDL increased by 2%
Intervention group

Table 3. Metabolic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Average</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 ± 2.6</td>
<td>25.3 ± 2.5*</td>
<td>-1.2 ± 2.1* (-5%)</td>
</tr>
<tr>
<td>Chol (mg/dl)</td>
<td>236 ± 34</td>
<td>213 ± 33*</td>
<td>-23 ± 28* (-10%)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>35.6 ± 6.7</td>
<td>36.2 ± 7.0</td>
<td>0.65 ± 5.1 (+2%)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>167 ± 21</td>
<td>152 ± 20*</td>
<td>-15 ± 21* (-8%)</td>
</tr>
<tr>
<td>Chol/HDL</td>
<td>6.9 ± 1.5</td>
<td>6.1 ± 1.5*</td>
<td>-0.8 ± 0.9* (-12%)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>169 ± 73</td>
<td>133 ± 54*</td>
<td>-36 ± 48 (-21%)</td>
</tr>
</tbody>
</table>

Control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Average</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>26.5 ± 2.1</td>
<td>26.4 ± 2.1</td>
<td>-0.1 ± 2.0 (0%)</td>
</tr>
<tr>
<td>Chol (mg/dl)</td>
<td>238 ± 34</td>
<td>233 ± 28</td>
<td>-3 ± 20 (+1%)</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>35.2 ± 6.0</td>
<td>36.0 ± 6.6</td>
<td>0.86 ± 4.4 (+2%)</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>160 ± 30</td>
<td>167 ± 25</td>
<td>8 ± 19 (-5%)</td>
</tr>
<tr>
<td>Chol/HDL</td>
<td>6.6 ± 1.1</td>
<td>6.7 ± 1.3</td>
<td>0.1 ± 1 (+2%)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>178 ± 92</td>
<td>149 ± 58</td>
<td>-30 ± 67 (-17%)</td>
</tr>
</tbody>
</table>

*p < 0.001 and tp < 0.05, significant difference, baseline versus average; tp < 0.001 and tp < 0.05, significant difference, intervention group versus control group. Unless otherwise indicated, values presented are mean values ± SD. Average = mean for total study period (3 weeks and 3.6.9 and 12 months); BMI = body mass index (weight/height²); Chol = cholesterol; HDL = high density lipoprotein; LDL = low density lipoprotein.

(p = NS). In the control group, body weight and lipids remained unchanged, with the exception of triglycerides, which decreased by 17% (p < 0.05). There was no significant correlation between changes in any metabolic variable and energy expenditure in physical activity.

Hemodynamic and respiratory variables (Tables 4 and 5, Fig. 4 and 5). Intervention group. Rest heart rate decreased from 74 ± 13 to 68 ± 10 beats/min (p < 0.05); VO₂ at ventilatory threshold and peak exercise increased by 7% from 1.09 ± 0.3 to 1.17 ± 0.3 liters/min (p < 0.001) and 14% from 1.85 ± 0.4 to 2.10 ± 0.5 liters/min (p < 0.05), respectively.

Control group. There was a slight decrease in VO₂ at ventilatory threshold by 8% from 1.12 ± 0.3 to 1.03 ± 0.4 liters/min (p < 0.05) and at peak exercise by 1% from 1.86 ± 0.4 to 1.85 ± 0.5 liters/min (p < 0.05).

Table 4. Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>12 Months</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR at rest (beats/min)</td>
<td>74 ± 13</td>
<td>68 ± 10*</td>
<td>-6 ± 168 (-9%)</td>
</tr>
<tr>
<td>Maximal HR (beats/min)</td>
<td>143 ± 17</td>
<td>150 ± 18*</td>
<td>7 ± 151 (+5%)</td>
</tr>
<tr>
<td>Maximal SBP (mm Hg)</td>
<td>188 ± 20</td>
<td>198 ± 20*</td>
<td>10 ± 251 (+5%)</td>
</tr>
<tr>
<td>Maximal RPP (10³)*</td>
<td>27.0 ± 4</td>
<td>29.7 ± 5</td>
<td>2.7 ± 64 (+106%)</td>
</tr>
<tr>
<td>Maximal exercise time (s)</td>
<td>575 ± 156</td>
<td>629 ± 145</td>
<td>54 ± 904 (+99%)</td>
</tr>
</tbody>
</table>

Control group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>12 Months</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR at rest (beats/min)</td>
<td>78 ± 11</td>
<td>79 ± 12</td>
<td>1 ± 13 (+1%)</td>
</tr>
<tr>
<td>Maximal HR (beats/min)</td>
<td>150 ± 17</td>
<td>149 ± 19</td>
<td>-1 ± 15 (0%)</td>
</tr>
<tr>
<td>Maximal SBP (mm Hg)</td>
<td>190 ± 25</td>
<td>184 ± 22</td>
<td>-6 ± 34 (-5%)</td>
</tr>
<tr>
<td>Maximal RPP (10³)*</td>
<td>28.5 ± 6</td>
<td>27.4 ± 5</td>
<td>-1.1 ± 6 (-4%)</td>
</tr>
<tr>
<td>Maximal exercise time (s)</td>
<td>564 ± 149</td>
<td>580 ± 143</td>
<td>16 ± 74 (+28%)</td>
</tr>
</tbody>
</table>

*p < 0.05, tp < 0.01 and tp < 0.001, significantly different from baseline; tp < 0.05 and tp < 0.001, significantly different from control group. Unless otherwise indicated, values presented are mean values ± SD. HR = heart rate; RPP = rate-pressure product; SBP = systolic blood pressure.

0.5 to 1.85 ± 0.5 liters/min (p < 0.05). A significant correlation (r = 0.58, p < 0.001) between the absolute change in ventilatory threshold VO₂ (liters/min) and the absolute change in maximal oxygen uptake (VO₂max) (liters/min) was observed (Fig. 4). A nearly identical increase in maximal respiratory exchange ratio could be detected in both groups (intervention group from 1.04 ± 0.1 to 1.15 ± 0.2; control group from 1.03 ± 0.1 to 1.14 ± 0.2), indicating a comparable contribution of anaerobic work between groups at initial and peak exercise.

Figure 4. Absolute change in oxygen uptake at ventilatory threshold (Vt) versus absolute change in maximal oxygen uptake (VO₂max). The change in ventilatory threshold within the observation period (1 year - beginning) is plotted against the change in VO₂max. There was a significant correlation between change in ventilatory threshold and VO₂max in patients in both groups.
final stress tests. After 1 year, rest heart rate, VO₂ at ventilatory threshold and peak exercise, exercise time at which ventilatory threshold occurred and peak exercise time, maximal heart rate and systolic blood pressure in the intervention group differed significantly from the corresponding variables in the control group.

Despite a significant improvement in maximal rate-pressure product, the number of positive ECG responses in the intervention group decreased from an initial 13 (45%) to 7 (24%) after 1 year, and fewer patients stopped the stress test because of progressive angina pectoris (17 vs. 14, p = NS). In the control group the number of positive ECG responses (10 vs. 12), and the number of patients with progressive angina pectoris (15 vs. 15) remained essentially unchanged.

There was a significant correlation between energy expenditure and absolute change in VO₂ at ventilatory threshold (liters/min) (y = 1,485 + 1,688x, r = 0.55, p < 0.001) as well as absolute change in VO₂max (liters/min) (y = 1370 + 1058x, r = 0.62, p < 0.001) (Fig. 5).

Coronary morphology (Table 6, Fig. 1). In all 62 patients follow-up angiograms were available at 12 months. An average of 3.0 ± 1.6 (range 1 to 7) stenoses were evaluated in each patient. Progression was noted in 29% (intervention group n = 18; control group n = 16) and regression in 16% (intervention group n = 8; control group n = 2). The difference between both groups reached statistical significance (p < 0.01).

There were seven new lesions in previously normal segments (intervention group n = 2; control group n = 5). Six in previously open vessels progressed to total occlusion (intervention group n = 1; control group n = 5), and five totally occluded segments (intervention group n = 4; control group n = 1) were recanalized.

There were no statistical differences among patients with progression, no change or regression of coronary artery disease with respect to age (progression 54 ± 6 years, no change 53 ± 6 years, regression 53 ± 8 years), Gensini score (progression 29 ± 16, no change 32 ± 18, regression 30 ± 23), left ventricular ejection fraction (progression 56 ± 8%, no change 58 ± 9%, regression 57 ± 10%) and the initial physical work capacity (progression 593 ± 173 s, no change 560 ± 131 s, regression 582 ± 152 s).

The best logistic multivariate model for estimation of the change in coronary morphology, expressed as a trichotomous variable (progression, no change and regression) included the energy expenditure in leisure time physical activity (p < 0.001) and change in LDL cholesterol (p < 0.01). Other variables, such as group assignment, age, smoking, change in body mass index, HDL cholesterol and triglycerides, did not contribute significantly to predictive value and therefore were eliminated from the logistic model.

There were two important messages emerge from this study: 1) Regular physical exercise delays the onset of the ventilatory threshold and improves VO₂max in patients with symptomatic coronary artery disease. To achieve this beneficial effect patients must be willing to expend ~1,400 kcal/week in some form of leisure time physical activity, which amounts to ~3 to 4 h/week in endurance training. 2) Achieving regression of coronary ath-
erosclerotic lesions is significantly more demanding with respect to physical activity. On average, 2,200 kcal/week must be expended, amounting to 5 to 6 h/week of regular physical exercise.

Respiratory and hemodynamic variables. Ventilatory threshold. The physiologic basis of ventilatory threshold, particularly with respect to lactate and anaerobic energy production, has been the subject of controversy (24,25). Nevertheless, as long as exercise mode and protocol are not changed, the ventilatory threshold is a reproducible, noninvasive index of the increase in blood lactate during exercise in normal subjects (26,27) and in patients with various heart diseases (25,28). The results of this study demonstrate that physical exercise at a specified intensity caused a delay in the onset of ventilatory threshold by an average of 71 ± 96 s (26); consequently, patients reached a small but significant decrease in ventilatory threshold and VO\textsubscript{2}max by an average of 7%. The amount of work accomplished between ventilatory threshold and peak exercise was nearly identical, suggesting a similar contribution of anaerobic work at baseline and at 1 year. Various peripheral adaptive mechanisms may account for this phenomenon: 1) a decrease in ventilatory threshold at a ventilatory threshold of 7%; 2) a decrease in lactate diffusion rate and respiratory sensitivity to carbon dioxide(32); 4) a decreased lactate diffusion rate and respiratory sensitivity to carbon dioxide (32). Thus, it must be assumed that in the present study aging attenuated respiratory and hemodynamic variables.

Maximal oxygen uptake and ventilatory threshold may be determined by two factors (Fig. 4 and 5, Table 7). First, the training intensity and frequency may affect the magnitude of alterations in these variables. The relatively low training frequency and intensity in studies of patients with symptomatic coronary artery disease (25) or healthy elderly subjects (27) may have contributed to the finding of an increased VO\textsubscript{2}max but unchanged ventilatory threshold after endurance training. In contrast, Davis et al. (26) reported an increase in VO\textsubscript{2} at ventilatory threshold and peak exercise of 44% and 25%, respectively, in healthy middle-aged men participating in a strenuous exercise program (3.1 h/week at ~80% of peak VO\textsubscript{2}). An increase in VO\textsubscript{2} at ventilatory threshold of 20% has also been observed in patients with chronic heart failure who exercised for an average of >4 h/week at a heart rate corresponding to 75% of peak VO\textsubscript{2} (28). These results in healthy people and patients with coronary disease support the finding of the present study that an improvement in functional capacity at submaximal work loads is only achievable by 3 to 4 h/week of endurance training.

Aging itself represents the second factor influencing the training response with respect to changes in VO\textsubscript{2} at ventilatory threshold and peak exercise. Several mechanisms seem to be responsible for this phenomenon: 1) a decrease in maximal achievable heart rate might account for both a decrease in ventilatory threshold and VO\textsubscript{2}max (25); 2) genetic endowments; 3) a shift from fast to slow twitch, predominantly glycolytic muscle fibers (31); 4) a decreased lactate diffusion rate and respiratory sensitivity to carbon dioxide (32). Thus, it must be assumed that in the present study aging attenuated the training effect with respect to ventilatory threshold and VO\textsubscript{2}max in the intervention group and may have contributed to the decrease in these variables in the control group.

### Table 7. Comparison of Relative Change in Oxygen Uptake at Ventilatory Threshold and Peak Exercise With Previously Published Studies

<table>
<thead>
<tr>
<th>Exercise and diet (present study)</th>
<th>Clinical Characteristics</th>
<th>Age (yr)</th>
<th>Vt (%)</th>
<th>VO\textsubscript{2}max (%)</th>
<th>Exercise/Interval (%VO\textsubscript{2}max)</th>
<th>Exercise/Frequency (h/wk*)</th>
<th>Study Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention (n = 29)</strong></td>
<td>Stable CAD</td>
<td>53 ± 6</td>
<td>+7*</td>
<td>+14*</td>
<td>75</td>
<td>3.3</td>
<td>1 yr</td>
</tr>
<tr>
<td><strong>Control (n = 32)</strong></td>
<td>Stable CAD</td>
<td>54 ± 7</td>
<td>-8</td>
<td>-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sullivan et al. (26)</td>
<td>Stable CAD</td>
<td>53 ± 8</td>
<td>-2</td>
<td>+1*</td>
<td>60</td>
<td>1.5</td>
<td>1 yr</td>
</tr>
<tr>
<td><strong>Control (n = 22)</strong></td>
<td>Stable CAD</td>
<td>53 ± 6</td>
<td>-10</td>
<td>-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davis et al. (26)</td>
<td>Sédentary men</td>
<td>43 ± 2</td>
<td>+44*</td>
<td>+25*</td>
<td>80</td>
<td>3.1</td>
<td>9 wk</td>
</tr>
<tr>
<td>Thomas et al. (27)</td>
<td>Sédentary men</td>
<td>39 ± 3</td>
<td>+5</td>
<td>+2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intervention (n = 45)</strong></td>
<td>Inactive</td>
<td>63 ± 6</td>
<td>+6</td>
<td>+18*</td>
<td>65-80</td>
<td>1.5</td>
<td>1 yr</td>
</tr>
<tr>
<td><strong>Control (n = 44)</strong></td>
<td>Inactive</td>
<td>62 ± 6</td>
<td>-1</td>
<td>+5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sullivan et al. (28)</td>
<td>Men with CHF</td>
<td>57 ± 6</td>
<td>+20!</td>
<td>+23†</td>
<td>75</td>
<td>4.1</td>
<td>16-24 wk</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, values presented are mean value ± SD. CAD = coronary artery disease; CHF = congestive heart failure; other abbreviations as in Table 5. *p < 0.05, significantly different from control group. †p < 0.05, significantly different from baseline.
Changes in coronary morphology. Regression of coronary atherosclerosis was noted in 8 patients (28%), 3 patients (10%) showed progression, and in 18 patients (62%) coronary morphology remained unchanged. Although on average no net regression of disease was achieved, no significant progression for the group as a whole could be detected. In contrast, the rate of progression in the control group within 1 year (4596) was comparable to rates of progression observed in previous studies (33,34).

A randomized study with combined colestipol/niacin therapy over 2 years in patients after aortocoronary bypass surgery Cholesterol Lowering Atherosclerosis Study (CLAS) (35) resulted in significant reduction in the average number of lesions with progression per patient, but average global score remained unchanged in the treatment group, whereas progression was noted in the placebo group. In contrast to our study and to the results of the CLAS, predominant and significant regression could be demonstrated in another randomized study (36) with lovastatin/colestipol and niacin/colestipol as lipid-lowering drugs. In the Lifestyle Heart Trial (7), regression of coronary atherosclerosis occurred in 82% of all patients participating in the intervention group (low fat vegetarian diet, moderate exercise, stress management, stopping smoking, group support) but also 42% of patients in the control group. In the recently published St. Thomas' Atherosclerosis Regression Study (37), a low fat diet led to rather normal lipoprotein levels and an overall retarded progression, of coronary artery disease, and overall increased regression of disease was achieved. These beneficial effects increased when cholestyramine was added to the regimen.

Physical activity level and regression of coronary artery disease. In this study progression of coronary lesions could be linked to the amount of leisure time physical activity performed, although even intensive physical activity did not grant immunity from progression of disease in all subjects. However, regression did not occur whenever intensity levels were lower than 1,600 kcal/week. Changes in metabolic variables, such as body weight, cholesterol, HDL cholesterol and triglycerides, were not significantly correlated with the degree of physical activity. Therefore, dietary changes in energy and fat consumption seem to contribute more to reduction in body weight and serum cholesterol than intensive physical exercise.

The amount of kilocalories spent in physical activity by patients in the control group (1,187 ± 97 kcal/week) was comparable to data from the Minnesota Heart Survey (19). In that study middle-aged men (45 to 65 years) were found to spend ~1,100 kcal/week during leisure time physical activity. Thus, even repeated counseling about the necessity of physical activity failed to change the life-style of patients not under strict supervision.

To determine which variables were independently associated with changes in coronary artery morphology, stepwise multiple linear regression analyses were performed using the risk characteristics described earlier in the Methods section as predictor variables. The independent predictors of changes in coronary morphology were changes in LDL cholesterol and physical activity levels. Although significantly correlated with progression rate, the group assignment failed to enter the logistic model in competition with the risk variables, probably because of the effect of the intervention on these risk variables during the study period.

Clinical implications. The results of this study imply that patients with stable coronary artery disease willing to devote their leisure time partly to intensive physical exercise are regularly rewarded with an upward shift of their anaerobic threshold during submaximal exercise. To achieve this goal, a minimum of 1,400 kcal/week must be expended; exercise performed at lower intensity levels, as in most rehabilitation programs, failed to change the position of the anaerobic threshold. With respect to leisure time physical activity and change in coronary morphology, three aspects are noteworthy: 1) In this study leisure time physical activity represents an independent predictor of change in coronary morphology. 2) Progression of coronary artery disease is negatively correlated with the amount of physical activity expended during leisure time. 3) Regression occurs only in motivated patients who are willing to spend an average of 2,200 kcal/week in leisure time physical activity. Nevertheless, progression of coronary artery disease was observed in some patients despite high activity levels and excellent compliance.

References


