Exercise training and myocardial remodeling in patients with reduced ventricular function: One-year follow-up with magnetic resonance imaging

Jonathan Myers, PhD, Ute Goebbels, MD, Gerald Dzeikan, MD, Victor Froelicher, MD, Jens Bremerich, MD, Peter Mueller, MD, Peter Buser, MD, and Paul Dubach, MD ***Chur and Basel, Switzerland, and Palo Alto, Calif***

Background Exercise training is now an accepted therapeutic intervention in patients with reduced ventricular function after a myocardial infarction. However, there are conflicting reports on the effects of training on the remodeling process of the heart, and previous studies have only assessed short-term effects of training.

Methods and Results Twenty-five patients with reduced ventricular function after myocardial infarction were randomly assigned to an intensive 2-month exercise training program or to a control group (control group: n = 13, aged 55 ± 7 years, ejection fraction 33.3% ± 6%; exercise group: n = 12, aged 56 ± 5 years, ejection fraction 31.5% ± 7%) and followed up for 1 year. Measures of left ventricular size, function, and wall thickness in the infarct and noninfarct areas were made by magnetic resonance imaging at baseline, after the 2-month training period, and 1 year later. Maximal oxygen uptake increased in the trained group, from 19.7 ± 3 mL/kg per minute at baseline to 25.1 ± 5 and 24.2 ± 5 mL/kg per minute after 2 months and 1 year, respectively ($P < .05$ vs baseline for both), whereas the control group did not change significantly. Ejection fraction, end-diastolic volumes, and end-systolic volumes did not change at any measurement point throughout the study period in either the trained or control groups. Myocardial wall thickness measurements at end-diastole and end-systole and their differences determined by magnetic resonance imaging yielded no significant interactions between groups. When myocardial wall thickness measurements were classified by infarct or noninfarct areas, no differences were observed between groups over the study period.

Conclusions Intensive exercise training in patients with reduced ventricular function resulted in a significant improvement in exercise capacity after 2 months, and this improvement was sustained over 1 year. In contrast to some recent reports, training had no deleterious effects on left ventricular volume, function, or wall thickness regardless of infarct area. (Am Heart J 2000;139:252-61.)

Before the 1990s, exercise training was generally considered contraindicated or was used selectively among patients with reduced ventricular function.[1,2] In recent years, training has become an accepted treatment modality for patients with reduced ventricular function. A number of randomized trials have shown that training not only improves exercise capacity[1-11] but reverses skeletal muscle metabolic derangements,[5,6,10] increases maximal cardiac output,[5,8,9] and improves measures of quality of life in these patients.[10,11] The 1995 Agency for Health Care Policy and Research guidelines stated that the available evidence strongly supports exercise training for stable patients with reduced ventricular function after a myocardial infarction or bypass surgery,[2] a recommendation that generally contrasts with those of the previous decade.

A topic that remains the source of some dispute, however, is the effect of training on the status of the left ventricle in such patients. The combination of myocardial wall thinning, aneurysm formation, expansion of the infarct area, and an increase in the radius of the left ventricle has been termed "myocardial remodeling" and together appears to represent an important prognostic marker after an infarction[12,13] and a precursor to heart failure.[14-17] Several animal studies have demonstrated further ventricular dilation with training after experimentally induced infarctions.[18,19] One study with echocardiography in human beings suggested that exercise training in patients with reduced left ventricular function after a myocardial infarction led to further myocardial damage, including wall thinning, infarct expansion, further asynergy, and a reduction in ejection fraction.[20] However, several subsequent controlled trials have failed to confirm these findings.[3,4,21,22]

We recently used magnetic resonance imaging (MRI)

From the Cardiology Divisions, Kantonsspital Chur and University Hospital; and the Veterans Affairs Palo Alto Health Care System and Stanford University.
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Reprint requests: Paul Dubach, MD, Kantonsspital Chur, CH 7000, Chur, Switzerland.

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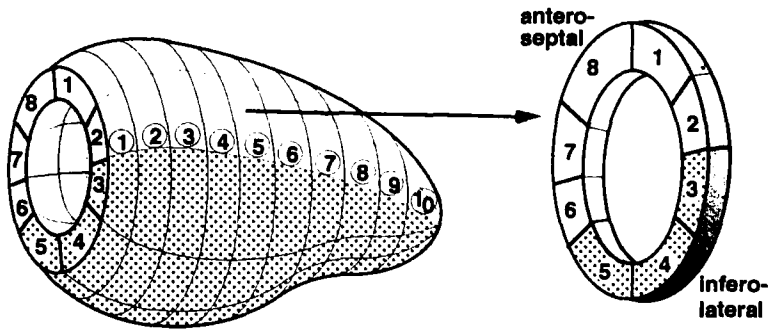
Figure 1



Cross-sectional and longitudinal MRI measurements. Each patient's myocardium was measured in consecutive short-axis tomograms composed of 8 segments each. These segments were divided into anteroseptal *(segments 1, 2, 6, 7,* and *8)* and inferolateral areas *(shaded segments 3, 4,* and *5).*

Table I. Patient characteristics at baseline

	Exercise group (n = 12)	Control group (n = 13)
Age (y)	56 ± 5	55 ± 7
Height (cm)	173 ± 7	168 ± 5
Weight (kg)	76.9 ± 7.5	70.2 ± 10.6
Ejection fraction (%)	31.5 ± 6.7	33.3 ± 5.8
Maximal oxygen uptake (mL/kg per minute)	19.4 ± 3	18.8 ± 3.9
Pulmonary function		
FEV_1 (1)	2.66 ± 0.45	2.66 ± 0.67
FEV_1 (% of normal)	80.4 ± 12	82.4 ± 22
Forced vital capacity (1)	3.69 ± 0.63	3.45 ± 0.9
Forced vital capacity (% of normal)	88.8 ± 11	85.9 ± 22
Peak expiratory flow (% of normal)	80.7 ± 25	76.9 ± 30
Medications		
Digoxin	8	7
Angiotensin-converting enzyme inhibitors	12	13
Diuretics	6	7
Others	3	5
Myocardial infarction		
Anterior	6	7
Inferior	4	3
Posterior	2	2
Risk factors1		
Smoking	11	11
Diabetes mellitus	1	1
Hyperlipidemia	7	4
Hypertension	7	5
Family history, coronary artery disease	7	9
Procedures		
Percutaneous transluminal coronary angioplasty	2	1
Coronary artery bypass surgery	9	11

to evaluate the effects of a short-term (2-month) high-intensity exercise training program on the left ventricular remodeling process in patients with reduced ventricular function.[3] We did not observe any differences in ventricular volumes, mass, function, or wall thickness in either the trained or the control groups. These findings are in agreement with 2 large randomized trials with echocardiography recently completed in Italy.[4,21] Although MRI has been shown to provide greater precision and reproducibility compared with other imaging techniques and provides 3-dimensional imaging not possible with echocardiography,[23-26] no studies have

Table II. Exercise and gas exchange data

	Exercise group			
	Test 1	**Test 2**	**Test 3**	**Test 4**
Rest				
Heart rate (beats/min)	94 ± 18	82 ± 16	79 ± 17	78 ± 8
Systolic blood pressure (mm Hg)	132 ± 18	133 ± 13	137 ± 13	141 ± 20
Diastolic blood pressure (mm Hg)	84 ± 11	80 ± 9	83 ± 12	90 ± 10
Lactate threshold				
Heart rate (beats/min)	117 ± 17	111 ± 20	113 ± 18	110 ± 10
Systolic blood pressure (mm Hg)	152 ± 19	155 ± 12	161 ± 14	167 ± 22
Diastolic blood pressure (mm Hg)	85 ± 12	78 ± 7	82 ± 17	95 ± 10
Oxygen uptake (mL/min)	1063 ± 222	1311 ± 309*	1437 ± 187†	1322 ± 286†
Oxygen uptake (mL/kg per minute)	13.6 ± 2.6	17.0 ± 3.7*	18.9 ± 2.2†	16.9 ± 3.7*
Minute ventilation	31.8 ± 6.7	39.1 ± 13.5	40.4 ± 5.7	36.7 ± 7.1
CO_2 production (mL/min)	952 ± 226	1224 ± 437	1329 ± 213	1225 ± 316
Respiratory exchange ratio	0.89 ± 0.09	0.91 ± 0.12	0.92 ± 0.09	0.9 ± 0.1
Lactate (mmol/L)	1.40 ± 0.29	1.46 ± 0.53	1.54 ± 0.41	1.4 ± 0.4
Exercise time (min)	4.82 ± 1.2	6.4 ± 2.0	7.3 ± 1.2†	6.6 ± 1.4
Perceived exertion	10.6 ± 2.3	10.4 ± 3.6	9.7 ± 1.5	1.8 ± 2.1
Watts	69.7 ± 17	90.0 ± 28	105.1 ± 16	95.9 ± 17
Maximal exercise				
Heart rate (beats/min)	144 ± 22	149 ± 20	150 ± 25	149 ± 16
Systolic blood pressure (mm Hg)	170 ± 23	187 ± 30	180 ± 23	202 ± 28
Diastolic blood pressure (mm Hg)	86 ± 13	85 ± 11	87 ± 18	101 ± 12
Oxygen uptake (mL/min)	1493 ± 260	1813 ± 389*	1872 ± 401*	1885 ± 372*
Oxygen uptake (mL/kg per minute)	19.4 ± 3.0	23.9 ± 4.8*	25.1 ± 4.8*	24.2 ± 4.8*
Minute ventilation	64.5 ± 12	79.8 ± 14.2*	77.2 ± 10.7	74.4 ± 16.0
CO_2 production (mL/min)	1788 ± 322	2291 ± 495*	2274 ± 463*	2262 ± 402
Respiratory exchange ratio	1.21 ± 0.3	1.27 ± 0.08	1.22 ± 0.06	1.20 ± 0.1
Lactate (mmol/L)	4.41 ± 1.09	5.64 ± 1.3*	5.64 ± 1.13*	2.8 ± 0.8
Exercise time (min)	9.38 ± 1.7	12.1 ± 1.9†	12.9 ± 2.0†	12 .0 ± 2.0†
Perceived exertion	18.7 ± 0.90	19.2 ± 0.55	18.8 ± 0.90	19.2 ± 0.9
Watts	129.0 ± 20	172.2 ± 32†	175.3 ± 31*	176.0 ± 27†

Test 1 represents baseline; test 2 is 1 month after random assignment to training or control; test 3 is completion of the 2-month training program; test 4 is 1 year after random assignment.
*$P < .05$ vs baseline within group.
†$P < .01$ vs baseline within group.

been performed with the use of this technology over a longer follow-up period (eg, 1 year). This longer period is of interest in the context of exercise training because of the limited data available in human beings on the time course of the remodeling process.

In the current study we reevaluated our patients 1 year after random assignment to either the aforementioned residential rehabilitation program or a control group. Maximal exercise testing with gas exchange and lactate analysis and MRI measures of ventricular volumes, mass, function, and wall thickness were performed. Our objective was to contrast the short- and long-term effects of exercise training on the remodeling process in patients with reduced ventricular function after a myocardial infarction.

Methods

Patients

Twelve male patients (mean age 56 ± 5 years) participated in the exercise group and 13 male patients (mean age 55 ± 7 years) participated in the control group after giving written informed consent. Clinical characteristics of the 2 groups are outlined in Table I. All patients had had a recent myocardial infarction, and their hospital course included the diagnosis of heart failure. Nine (75%) of the 12 patients in the exercise group and 11 (85%) of the 13 patients in the control group underwent bypass surgery after myocardial infarction. Before hospitalization, none of the patients had a history of heart failure. The presence of heart failure was documented by signs, symptoms, and angiographic evidence of reduced left ventricular function (ejection fraction <40%) caused by coronary artery disease. All patients had stable symptoms after myocardial infarction, surgery, or both before random assignment. The duration between the myocardial event and the initial test was 36.1 ± 14 days for patients randomly assigned to the trained group and 35.0 ± 6 days for the control group. All were limited by fatigue or dyspnea on baseline exercise testing, and none had clinical evidence of pulmonary disease.

Study design

Group assignment was random. Patients in both groups underwent nuclear magnetic resonance evaluations at random

Control group				*P* value between groups
Test 1	Test 2	Test 3	Test 4	
91 ± 13	84 ± 12	84 ± 13	72 ± 12	.66
137 ± 18	131 ± 19	136 ± 19	140 ± 24	.79
83 ± 10	80 ± 11	78 ± 10	88 ± 13	.76
115 ± 14	106 ± 10	108 ± 13	106 ± 16	.93
167 ± 23	151 ± 26	152 ± 22	158 ± 27	.56
84 ± 11	79 ± 14	79 ± 11	94 ± 17	.85
956 ± 225	891 ± 282	831 ± 147	946 ± 222	<.01
13.7 ± 2.9	12.4 ± 3.0	11.8 ± 2.0	12.9 ± 3.6	<.001
28.8 ± 7.3	26.2 ± 6.4	24.1 ± 3.5	25.4 ± 6.1	.02
953 ± 337	846 ± 316	740 ± 144	850 ± 242	<.01
0.95 ± 0.08	0.94 ± 0.09	0.90 ± 0.07	0.89 ± 0.09	.40
1.61 ± 0.48	1.51 ± 0.53	1.34 ± 0.43	1.5 ± 0.6	.34
5.0 ± 1.6	4.85 ± 1.7	4.54 ± 1.2	4.6 ± 1.6	<.01
11.2 ± 2	11.3 ± 2.6	11.2 ± 1.7	10.6 ± 1.9	.86
63.8 ± 25	61.2 ± 23	56.5 ± 14	58.2 ± 19	<.01
141 ± 17	142 ± 16	141 ± 17	133 ± 25	.90
176 ± 28	182 ± 28	176 ± 22	181 ± 34	.73
89 ± 10	87 ± 13	91 ± 16	98 ± 17	.97
1314 ± 270	1414 ± 309	1363 ± 264	1432 ± 391	.20
18.8 ± 3.9	20.0 ± 4.0	19.8 ± 4.3	19.5 ± 5.8	.13
51.5 ± 10.3	56.1 ± 9.2	53.4 ± 11.6	52.7 ± 14.4	.15
1616 ± 349	1782 ± 425	1663 ± 422	1718 ± 430	.13
1.23 ± 0.11	1.26 ± 0.15	1.22 ± 0.12	1.20 ± 0.3	.54
4.63 ± 1.28	4.45 ± 1.48	4.9 ± 1.9	2.8 ± 1.1	.25
9.1 ± 2.0	10.0 ± 2.0	10.7 ± 2.1	9.4 ± 2.7	.04
18.9 ± 0.92	19.0 ± 0.78	18.7 ± 0.91	19.2 ± 0.8	.66
113.5 ± 27	124.6 ± 27	120.7 ± 29	117 ± 33	.04

assignment, after 2 months' participation in either exercise training or usual care, and after 1 year. Cardiopulmonary exercise testing and pulmonary function tests were also performed at these time points.

Exercise training

After stabilization and initial testing, patients in the exercise group resided in a rehabilitation center in Seewis, Switzerland, for a period of 8 weeks. Seewis is a small village in the mountains with an elevation of 3500 feet. The center has its own staff of physicians, consisting of a medical director and 3 interns/residents. Program components included education, exercise, and low-fat meals prepared 3 times daily by the center's cook. Two outdoor walking sessions daily for a duration of approximately 1 hour each were performed, once in the morning and once in the afternoon. Walking intensity was stratified into 4 levels on the basis of clinical status, exercise capacity, and performance on a 500-m walking test (50-m increase in altitude) on a nearby hill. The patients were accompanied by a physician during these walking sessions. Exercise leaders carried 2-way radios for communication with the center in case of emergency. A van equipped with emergency equipment followed the group.

In addition to these walking periods, the 12 patients in the exercise group performed four 45-minute periods of monitored stationary cycling per week. The cycling sessions were designed to elicit an intensity equal to roughly 60% to 70% of the patient's peak $\dot{V}O_2$ and were increased progressively over the 2 months as tolerated. Each of these sessions was monitored closely by a medical resident at the rehabilitation center. Heart rate, workload, and perceived exertion were recorded every 5 minutes; adjustments were made in exercise intensity as appropriate. Control patients received usual clinical follow-up. After the initial 2-month exercise training or control period, both groups were encouraged to remain physically active over the subsequent 10 months, although no formal program was implemented.

Quantification of physical activity

After the 2-month training or control period, occupational and recreational physical activities were quantified over the subsequent 10 months. At the 1-year visit, each patient responded to a physical activity questionnaire modified from that developed by Paffenbarger et al[27] used in the Harvard Alumni studies. Activities were quantified by the use of blocks walked or flights of stairs climbed per day, and occupational and recreational activities were classified as daily time spent in light, moderate, or vigorous energy expenditure.

Exercise testing

Maximal exercise tests were performed at baseline (approximately 1 month after myocardial infarction) and 1 month, 2 months, and 1 year after random assignment to the training or control group. On the day of testing, patients in both groups were requested to abstain from food, coffee, and cigarettes for 3 hours before the test. Standard pulmonary function tests were performed. Maximal exercise testing was performed on an electrically braked cycle ergometer with an individualized ramp protocol. Briefly, this test entails choosing an individualized ramp rate to yield a test duration of approximately 10 minutes.[28] Arterial blood lactate samples were drawn every minute throughout the test. A 12-lead electrocardiogram was monitored continuously, and blood pressure was measured manually every minute during exercise and throughout the recovery period. The patient's subjective level of exertion was quantified every minute by use of the Borg 6-20 scale.[29] All tests were continued to volitional fatigue/dyspnea. Respiratory gas exchange variables were acquired continuously throughout exercise with the Schiller CS-100 metabolic system. Gas exchange variables analyzed were oxygen uptake, carbon dioxide production, minute ventilation, respiratory rate, tidal volume, oxygen pulse, and respiratory exchange ratio. The lactate threshold was chosen by use of a plot of the minute-by-minute lactate responses versus time by 2 experienced observers.

Magnetic resonance imaging

Cine-MRI was performed with a commercially available 1.5-T MRI scanner in the supine position. Electrocardiographic electrodes were placed on the back to obtain an optimal electrocardiographic signal. Using T1-weighted spin-echo

sequences, the angulation of the left ventricular long-axis view was defined in a transverse and in a parasagittal scout image. The left ventricular short-axis view was defined as imaging planes perpendicular to the left ventricular long axis. The 4-chamber view was defined as an imaging plane encompassing the insertion of the anterior mitral leaflet and the apex in an oblique coronal view. Cine-MRI was performed with conventional nonsegmented (non-breath hold) electrocardiographically gated gradient refocused echo sequences with a flip angle of 30 degrees and an echo time of 6 ms. Slice thickness was 8 mm, and 14 to 16 frames per R-R interval were acquired in a single imaging plane. The whole heart was continuously encompassed from the base to the apex in a short-axis view, and 4 additional cine-MRI sequences were performed in the 4-chamber view, thus allowing for correction of partial volume effects and for regional wall motion analysis of the apex. Total imaging time was 20 minutes.

To obtain reproducible contrast between muscle and blood, a statistical analysis of pixel intensities with subsequent adaptation of the dynamic range (window and level of gray scale) was performed automatically. This permitted alterations in contrast between myocardium and blood pool to be minimized as well as differences in display parameters on images between the 2 MRI studies in each patient. For images with poor contrast (approximately 30% of the images), manual adjustment of the intensity level and width were performed subjectively to recognize the internal ventricular morphology.

All cine-MRIs were analyzed by a cardiologist and a radiologist who had extensive experience with cardiovascular MRI and who were blinded to the random assignment of the patients. In all cine-MRI loops, regional wall motion and global left ventricular ejection fraction were visually estimated by both investigators. In addition, regional systolic wall thickening was measured in 8 segments of the left ventricular myocardium in all short-axis planes, as previously described.[30] Left ventricular volumes were calculated as the sum of the measured cavity area times slice thickness of all slices covering the left ventricle. Left ventricular mass was obtained by calculating the endocardial and epicardial borders at end-diastole and end-systole, the left ventricular cavity areas, and the specific myocardial gravity (1.05). The papillary muscles were not included in the left ventricular mass. Left ventricular stroke volume and ejection fraction were calculated from end-systolic and end-diastolic volumes. Interobserver and intraobserver variability in our laboratory has been shown to be 6.6% ± 3.2% and 5.1% ± 2.9%, respectively, for left ventricular end-diastolic volume and 6.2% ± 3.3% and 4.8% ± 2.2%, respectively, for left ventricular mass. These values are similar to those recently reported elsewhere with the use of MRI.[25]

The myocardium was measured in consecutive short-axis tomograms encompassing the entire left ventricle. Each tomogram was divided into segments around the circumference as illustrated in Figure 1 (typically yielding 80 segments per heart). All slices that were necessary to encompass the entire left ventricle from base to apex were included in the analysis. No basal slices were discarded. Typically, 10 consecutive short-axis tomograms with a thickness of 8 mm each were required. Myocardial wall thickness was quantified in each segment at end-diastole and end-systole, and the difference (end-systolic minus end-diastolic wall thickness) was determined. The infarct areas that were predominantly anteroseptal (short-axis segments 1, 2, 6, 7, and 8) were summed to determine whether training caused thinning or thickening in an infarct-related or non-infarct-related area. Likewise, among patients who had an infarct that was predominantly inferolateral, segments 3, 4, and 5 were summed, and differences between infarct and noninfarct areas were determined.

Statistics

Statistical Graphics Corporation Software (Bethesda, Md) was used to perform multivariate analysis of variance procedures comparing hemodynamic, gas exchange, and MRI results between groups. Post hoc multiple comparison procedures were performed with the Scheffe method. Data are presented as mean ± SD.

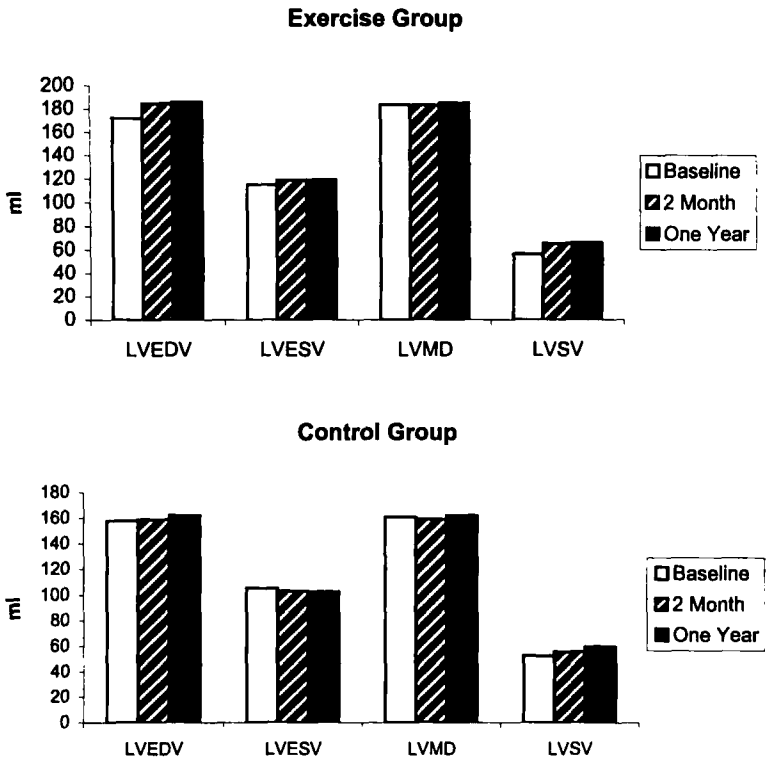
Results

No differences were observed between the 2 groups initially in clinical or demographic data, including age, height, weight, resting blood pressure, pulmonary function, ejection fraction, or maximal oxygen uptake (Table I). No untoward events occurred during any of the exercise testing or training procedures during the initial 2 months of observation. During the subsequent 10 months, 2 patients in the control group were hospitalized for decompensation of heart failure; both were stabilized after a brief uncomplicated hospital stay, returned to normal activities, and completed their 1-year visits. One patient in the exercise group had sudden cardiac death 9 months after beginning the study. Patients in the exercise group were closely monitored by heart rate, workload, and perceived exertion during their stationary cycling sessions and only generally during walking sessions. During monitored cycling over the 2-month training period, the mean percentage of maximal heart rate maintained was 83% ± 6%, the mean percentage of maximal workload was 78% ± 7%, and perceived exertion averaged 15.2 ± 2.

Maximal exercise testing

Exercise and ventilatory gas exchange data on the 4 exercise tests for each group are presented in Table II. Both groups achieved mean maximal respiratory exchange ratios of ≥1.20 and mean perceived exertion levels of approximately 19 on all 4 tests, which suggests that maximal efforts were generally achieved. No differences were observed within or between groups in maximal heart rate or blood pressure. The exercise group demonstrated a 26% increase in maximal oxygen uptake from test 1 to test 2 (19.3 ± 3.0 to 23.9 ± 4.8 mL/kg per minute, $P < .01$) and a further 5% increase from test 2 to test 3. After 1 year, these increases were generally maintained; maximal oxygen uptake was 25% higher versus baseline at 1 year ($P < .01$). Concomitant increases in maximal minute ventilation, CO_2 production, exercise time, and watts achieved were observed in the exercise group. No differences between tests

Figure 2



Left ventricular end-diastolic volume (*LVEDV*), end-systolic volume (*LVESV*), mass (*LVMD*, in grams, end diastole), and stroke volume (*LVSV*) measured at baseline, after 2 months, and at 1 year in exercise and control groups.

were observed among control patients in maximal oxygen uptake, exercise time, or watts achieved.

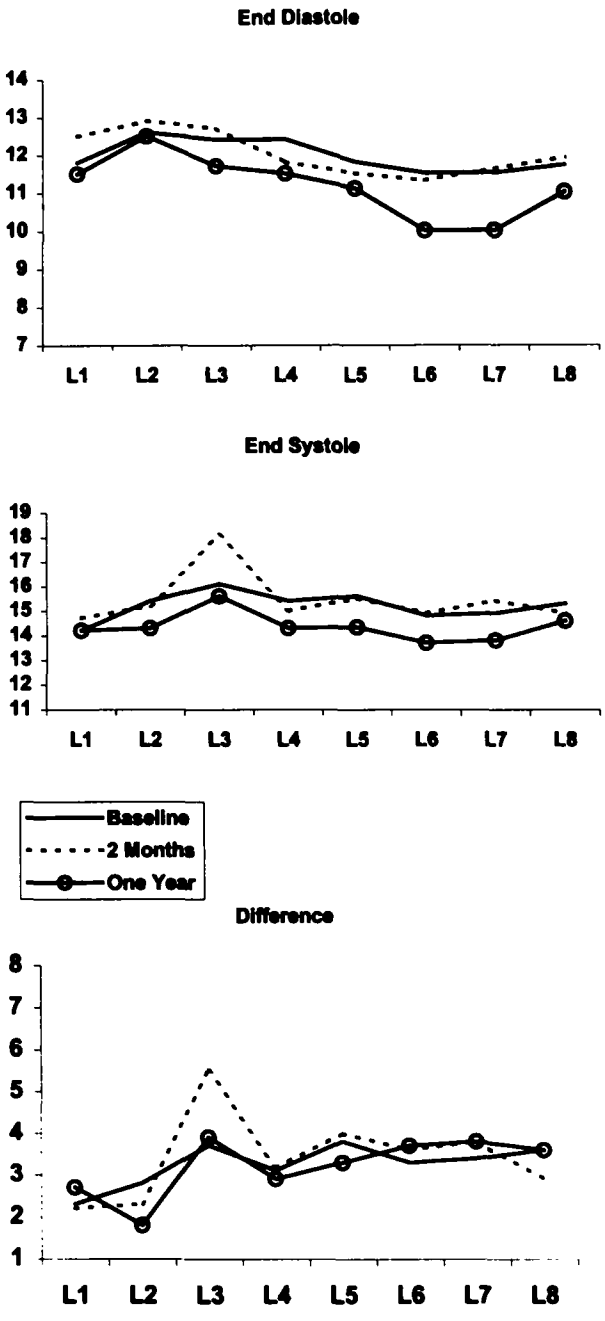
Oxygen uptake at the lactate threshold increased significantly during the training period in the exercise group (35% overall from test 1 to test 3). At 1 year, oxygen uptake at the lactate threshold remained 24% higher compared with baseline ($P < .01$). Conversely, small but insignificant decreases were observed among control patients (Table II). Similar increases in exercise time and watts achieved at the lactate threshold were observed among patients in the exercise group, whereas the control group demonstrated small decreases in these variables. No differences were observed within or between groups in heart rate, systolic or diastolic blood pressure, minute ventilation, CO_2 production, respiratory exchange ratio, lactate, or perceived exertion at this point.

MRI of the left ventricle

Left ventricular volume, mass, and ejection fraction values in the 2 groups are presented in Figure 2. There were no differences observed within or between groups in end-systolic or end-diastolic volumes, mass, or stroke volume during the study period. Likewise, changes in ejection fraction were similar between groups (35.3% ± 9% at baseline versus 36.4% ± 10% at 2 months and 35.0% ± 8% at 1 year in the exercise group and 36.0% ± 10% at baseline versus 38.3% ± 13% at 2 months and 38.0% ± 12% at 1 year in the control group).

The MRI data were summed by infarct-related and non-infarct-related segments among the anteroseptal and inferolateral infarct groups (Figure 1). The infarct areas for the patients with anteroseptal infarct in the trained group are presented in Figure 3, and those for control patients are presented in Figure 4. No significant differences were observed between exercise and control groups in end-diastolic wall thickness, end-systolic wall thickness, or their difference in either the infarct or noninfarct areas. Although the inferolateral groups were smaller (4 patients in the exercise group and 3 in the control group), the myocardial wall thickness measurements in these patients were also similar between groups throughout the study period.

Figure 3



Myocardial wall thickness (mm, ±SD) among patients with anteroseptal infarct in infarct areas, summed for each of 8 cross-sectional segments, in exercise group.

Physical activity

Patients in the exercise group engaged in more physical activity classified as "vigorous" relative to control patients during the 10-month period after completing the training program. Time spent during vigorous activity was approximately 2100 kcal/wk greater in the exercise group relative to control patients ($P < .05$), whereas time spent during moderate activities and energy expended by blocks walked/stairs climbed was similar between groups.

Discussion

A multitude of studies have been published documenting the beneficial effects of exercise training among patients who have had a myocardial infarction,[1,2] and this modality has recently been expanded to include patients who have reduced ventricular function.[3-11] The majority of studies have reported results based on the typical model of cardiac rehabilitation, for example, programs lasting 1 to 3 months, and few data exist as to patient outcomes the year after the program has been completed. In the current study, we were interested in (1) the extent to which gains and functional capacity achieved during rehabilitation were maintained over 1 year; (2) clinical outcomes, such as hospitalizations, coronary events, or deaths during this period; and in particular, (3) whether remodeling of the left ventricle known to occur over the year after a myocardial infarction was influenced by exercise training and subsequent physical activity patterns.

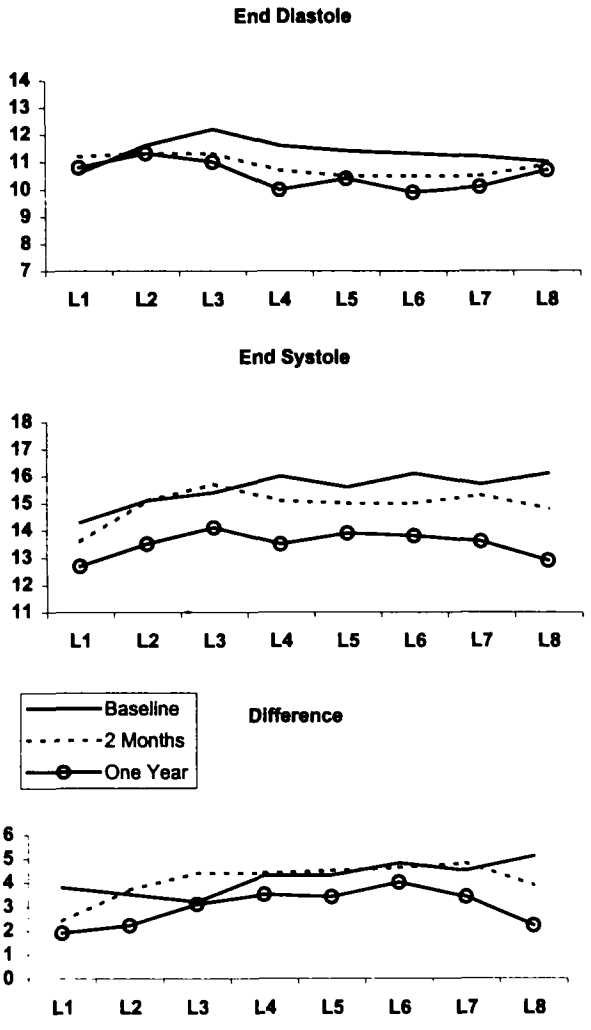
The results from this study suggest that (1) among patients with reduced ventricular function after a myocardial infarction, a concentrated high-intensity exercise training program yielded substantial increases in exercise capacity in the short term, and these improvements were maintained over 1 year; (2) there were no short-term effects of training on left ventricular mass, volume, function, or wall thickness determined by MRI; and (3) the status of the left ventricle by these measures was maintained over the subsequent year. To our knowledge, this is the first study to use MRI technology to study the effects of training on the myocardial remodeling process over 1 year. The use of MRI is a novel approach to quantify the remodeling process; relative to nuclear and echocardiographic techniques, MRI has been shown to yield greater reproducibility,[24-26] and unlike the other techniques it is capable of 3-dimensional imaging.[23]

It is generally recognized that remodeling of the left ventricle, including the degree of left ventricular dilatation, changes in the size of the infarction, and changes in wall thickness, for example, thinning of the infarct area and compensatory thickening in the noninfarct areas, are crucial factors influencing survival after an infarction.[12-17] The known factors that affect these processes include the site and extent of the infarction, the presence of continued ischemia, and angiotensin-converting enzyme inhibition.[20,31-35] The role of exercise training in this process has recently been disputed, with some studies demonstrating a worsening of the

remodeling process as a result of training,[18-20,36] others demonstrating no change,[3,4,37,38] and 1 randomized trial demonstrating that training actually attenuated the abnormal remodeling changes that occurred in control patients.[21] Animal studies have generally addressed only short bouts of training (ie, 1 to 4 weeks),[18,37,38] and human studies have addressed periods ranging from 2 to 6 months.[3-8,20,21,39] It has been demonstrated, however, that in some patients with reduced ventricular function, ventricular dilation progresses 1 year or longer after a myocardial infarction, with concomitant decreases in cardiac index, stroke index, and ejection fraction and increases in pulmonary wedge pressure and systemic vascular resistance.[40,41] Thus it is of interest to address these myocardial adaptations to exercise training up to 1 year after infarction and the effects that physical activity patterns may have on them.

In response to the suggestion that training may cause a worsening of global and regional myocardial function after an anterior myocardial infarction,[20] Giannuzzi et al[4] completed a multicenter controlled trial of exercise training in Italy. After 6 months, patients in both the trained and control groups whose ejection fractions were ≤40% demonstrated some degree of additional global and regional dilation. Importantly, however, training had no effect on this response, and there was no effect in either group among patients with ejection fraction >40%. More recently, these investigators completed a larger randomized trial in patients with left ventricular dysfunction after a myocardial infarction.[21] After 6 months, patients in the control group demonstrated increases in both end-systolic and end-diastolic volumes and a worsening in both wall motion abnormalities and regional dilatation relative to patients in the exercise group. The latter study was the first to suggest that an exercise program may actually attenuate abnormal remodeling in patients with reduced ventricular function. In contrast to the studies by Giannuzzi et al,[4,21] we did not observe that training had either a detrimental or an attenuating effect on the remodeling process despite similar effects of training (exercise capacity increased 29% in both studies after training). Our population was also similar to those of the former studies in that patients were randomly assigned roughly 1 month after a myocardial infarction, and the degree of left ventricular dysfunction was similar (mean ejection fraction ranged from 32% to 34% in exercise and control groups in both studies). Although the training period in the Giannuzzi et al[4] study lasted 6 months, only the first 2 months were supervised (as in our study), with the remainder being home-based. In the current study, the residential rehabilitation program provided a "captive" environment within which patients were trained at a high intensity, and compliance was optimized. Unlike previous studies in similar populations in which most of the increase in peak $\dot{V}O_2$ was attributable to subgroups of patients,[7,9,39,42] all of our subjects randomly assigned to the exercise group had improved peak $\dot{V}O_2$.

Figure 4



Myocardial wall thickness (mm, ±SD) among patients with anteroseptal infarct in noninfarct areas, summed for each of 8 cross-sectional segments, in exercise group.

Our findings also are in agreement with 3 other recent controlled trials in that no abnormal changes in wall thickness, wall motion, ventricular volumes, or ejection fraction were observed in either the trained or control groups after short-term training.[7,22,43] We previously observed that short-term, high-intensity training (2 months) does not cause any detrimental changes in myocardial remodeling.[3] In the current study, we extended the observations of the former studies by reevaluating our patients 1 year after myocardial infarc-

tion (9 to 10 months after completing the training program) and found no further global or regional changes in wall thickness, ventricular volumes, function, or mass. The suggestion that exercise training has the potential to adversely alter ventricular size and function[18-20] has had an impact on clinical practice, leading some researchers to suggest that patients with reduced ventricular function should not engage in this treatment modality. Taking the available data as a whole, however, such caution would not appear to be warranted. Although some provocative data have been published describing adverse effects of training on the hearts of animals, including severe global left ventricular dilation, left ventricular shape distortion, and scar thinning,[18,19] the bulk of the available data in human beings does not suggest that training causes any harmful effects on the myocardial remodeling process.[3,4,7,21,22] In fact, the available controlled studies demonstrate that training yields marked improvements in exercise tolerance and quality of life,[3,4,9-11] and there are recent data demonstrating that training may even benefit cardiac function[4,5] or attenuate abnormal remodeling.[21]

Because weekly energy expenditure has been demonstrated to reduce morbidity and mortality rates from coronary heart disease,[27] the activity patterns of patients after a myocardial infarction and their effect on cardiac size and function are of interest. Although rehabilitation programs for patients who have had a myocardial infraction generally last 1 to 3 months, the ideal model of comprehensive rehabilitation[1,2,4-6] is one in which patients gain exercise and lifestyle habits that would last indefinitely. This would be a particularly important goal in a residential rehabilitation program such as that used in the current study, in which education was an integral component of the program. Because reimbursement for cardiac rehabilitation rarely extends beyond 2 months, few data are available on the long-term effects of a rehabilitation program on patients' exercise habits. Hambrecht et al[45] reported that patients who expended an average of 1400 kcal/wk during leisure-time physical activity demonstrated increases in cardiorespiratory fitness over a 12-month period, and those expending approximately 2200 kcal/wk showed regression of angiographic coronary disease. In the current study, we observed that patients randomly assigned to the exercise group did indeed engage in a greater degree of recreational physical activity during the subsequent year relative to control patients (by approximately 2100 kcal/wk). Presumably, this had some influence on these patients maintaining the higher peak $\dot{V}O_2$ over the observation period. Importantly, these greater activity levels also had no adverse effects on myocardial mass, wall thickness, or function in patients with ventricular damage at baseline.

Summary

The current data confirm that exercise training in patients with reduced left ventricular function after a myocardial infarction is effective in improving exercise capacity and supports the recent Agency for Health Care Policy and Research recommendations that this modality is a useful adjunct to medical therapy in these patients.[2] In contrast to some recent reports, training did not cause further myocardial damage (ie, wall thinning, infarct expansion, changes in ejection fraction, or increases in ventricular volume), nor were there any long-term changes in these measures assessed with MRI. The application of MRI represents a significant advance in precision over previous studies, and to our knowledge, no study has evaluated the effects of training or physical activity status on these myocardial adaptations as long as 1 year after infarction. Our findings may be limited to the type of patients enrolled (patients with initial diagnosis of reduced ventricular function after an infarction and able to tolerate relatively high levels of training). In many patients, bypass surgery was performed after myocardial infarction, and this may have influenced the remodeling process through pericardial or mediastinal constraint. Last, because studies have suggested potentially important roles of the type and size of infarction and the time course of training (early or late after infarction) on the remodeling process,[17,19] future studies should be directed to address these issues further.

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