EXERCISE TRAINING increases maximal exercise capacity, endurance, and the minimal work rate required to induce myocardial ischemia in patients with coronary artery disease. These effects have been attributed to adaptations in skeletal muscle and the autonomic nervous system that result in smaller increases in heart rate and systolic blood pressure, and therefore in a reduced myocardial $O_2$ requirement, at any given submaximal exercise intensity. The results of previous studies have suggested that exercise training does not improve myocardial blood supply and left ventricular contractile function at the same myocardial $O_2$ requirement in patients with coronary artery disease. However, in experimental animals training has been shown to reduce myocardial ischemia and improve myocardial blood supply and left ventricular contractile function.

One explanation for this difference may be that an insufficient training stimulus was used in previous clinical studies. Our recent experience with the effects of prolonged, high-intensity training is consistent with this view. We have found that, in addition to peripheral adaptations, long-term exercise training of progressively increasing duration, frequency, and intensity can elicit further adaptations suggestive of improvement in myocardial ischemia and left ventricular...
function, as reflected by less ST segment depression at the same rate-pressure product and a higher stroke volume at a comparable heart rate and peripheral vascular resistance. The purpose of the present study was to test the hypothesis that prolonged and intense endurance exercise can improve left ventricular contractile function in patients with coronary artery disease.

Methods

Patients. Twenty-five patients with coronary artery disease who had an abnormal left ventricular exercise response before training completed 12 months of endurance exercise training. This group consisted of 24 men and one woman with an average age of 52 ± 2 years (mean ± SE). All of the patients provided written consent, and the study protocol was approved by the Human Studies Committee of Washington University. An abnormal left ventricular exercise response was defined as a change in ejection fraction from rest to exercise of 5% or less and/or development of discrete systolic regional wall motion abnormalities with exercise. Coronary artery disease was documented by unequivocal prior myocardial infarction and/or effort angina with angiographically proven fixed coronary artery stenosis. Of the 25 study patients, 22 had sustained a prior myocardial infarction, and 10 had chronic stable effort angina. Four had undergone coronary revascularization, one with recurrence of angina and two with myocardial infarction after surgery but before enrollment in the study. The interval between the major coronary event (myocardial infarction or coronary revascularization) and enrollment in the study was at least 3 months and averaged 11 ± 3 months. Two patients had left bundle branch block (LBBB); LBBB was persistent in one patient (No. 11, table 1) and induced by exercise (rate dependent) in the other (No. 12, table 1). Two patients had a left ventricular aneurysm (Nos. 10 and 24, table 1). Of the 14 patients who had coronary angiography, four had triple-vessel disease, six double-vessel disease, and four single-vessel disease. Seventeen patients were taking β-adrenergic–blocking agents, 10 long-acting nitrates, four calcium antagonists, and two patients were taking digoxin.

TABLE 1
Effects of exercise training on left ventricular function

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age/ gender</th>
<th>Rest</th>
<th>Peak exercise</th>
<th>Change</th>
<th>Peak exercise (RPP × 10³)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>1</td>
<td>42/M</td>
<td>49</td>
<td>59</td>
<td>34</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>46/M</td>
<td>54</td>
<td>46</td>
<td>51</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>51/M</td>
<td>52</td>
<td>48</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>54/M</td>
<td>45</td>
<td>58</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>55/M</td>
<td>63</td>
<td>65</td>
<td>65</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>43/M</td>
<td>53</td>
<td>58</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>7</td>
<td>62/M</td>
<td>21</td>
<td>20</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>8</td>
<td>39/M</td>
<td>61</td>
<td>64</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>50/M</td>
<td>43</td>
<td>43</td>
<td>47</td>
<td>45</td>
</tr>
<tr>
<td>10</td>
<td>63/M</td>
<td>43</td>
<td>45</td>
<td>41</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>64/M</td>
<td>29</td>
<td>30</td>
<td>29</td>
<td>19</td>
</tr>
<tr>
<td>12</td>
<td>69/M</td>
<td>73</td>
<td>73</td>
<td>73</td>
<td>76</td>
</tr>
<tr>
<td>13</td>
<td>56/M</td>
<td>55</td>
<td>55</td>
<td>53</td>
<td>56</td>
</tr>
<tr>
<td>14</td>
<td>46/M</td>
<td>53</td>
<td>58</td>
<td>56</td>
<td>59</td>
</tr>
<tr>
<td>15</td>
<td>64/M</td>
<td>50</td>
<td>43</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>16</td>
<td>60/M</td>
<td>44</td>
<td>44</td>
<td>42</td>
<td>51</td>
</tr>
<tr>
<td>17</td>
<td>55/M</td>
<td>57</td>
<td>64</td>
<td>47</td>
<td>61</td>
</tr>
<tr>
<td>18</td>
<td>55/M</td>
<td>64</td>
<td>73</td>
<td>60</td>
<td>73</td>
</tr>
<tr>
<td>19</td>
<td>57/M</td>
<td>60</td>
<td>56</td>
<td>49</td>
<td>59</td>
</tr>
<tr>
<td>20</td>
<td>59/M</td>
<td>61</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>21</td>
<td>34/F</td>
<td>64</td>
<td>60</td>
<td>63</td>
<td>72</td>
</tr>
<tr>
<td>22</td>
<td>38/M</td>
<td>60</td>
<td>70</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>23</td>
<td>56/M</td>
<td>51</td>
<td>70</td>
<td>69</td>
<td>72</td>
</tr>
<tr>
<td>24</td>
<td>61/M</td>
<td>31</td>
<td>32</td>
<td>28</td>
<td>35</td>
</tr>
<tr>
<td>25</td>
<td>31/M</td>
<td>66</td>
<td>66</td>
<td>67</td>
<td>75</td>
</tr>
<tr>
<td>Mean</td>
<td>52</td>
<td>53</td>
<td>54</td>
<td>52</td>
<td>58</td>
</tr>
<tr>
<td>± SE</td>
<td>±2</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
<td>±3</td>
</tr>
</tbody>
</table>

Controls

Mean 48.4 52 54 52 53 −0.4 −1.4 24.36 23.94
± SE ±2 ±3 ±3 ±3 ±1 ±1 ±0.88 ±0.84

EF = ejection fraction; RPP = rate-pressure product.

a p < .01, compared with EF at rest; b p < .001, compared with initial peak exercise EF; c p < .005, initial vs final; d p < .001, initial vs final.
The medications and their dosages were constant throughout the study except in one patient in whom the dose of propranolol was reduced. In this patient, propranolol was adjusted to the initial dosage for 10 days before final evaluation. The interval between the last dose of medication and the exercise test was also similar for each patient and averaged 13.8 ± 2 hr initially and 13.2 ± 2 hr (p = NS) at the end of the study.

Sixteen of the 25 patients, 53 ± 2 years old, had exercise-induced myocardial ischemia evidenced by effort angina, 0.1 mV or greater horizontal or downsloping ST segment depression, and/or discrete severe regional left ventricular contraction abnormalities during exercise. Eight patients, 49 ± 4 years old, all with a previous myocardial infarction, did not exhibit exercise-induced ischemia. One patient could not be classified because of LBBB and extensive myocardial scar (No. 11, table 1).

An additional group of patients who did not exercise was used to evaluate the reproducibility of the measurements and the likelihood of spontaneous improvement in left ventricular function over a 12 month period. It comprised 13 men and one woman (average age 48 ± 2 years) with documented coronary artery disease who were eligible for enrollment in our exercise program and similar to the training group in terms of age, maximal exercise capacity, and ejection fraction (table 1). These patients lived too far away or had schedule conflicts that prevented them from participating in the exercise program. Eleven of these patients had sustained prior myocardial infarction. Five had chronic stable effort angina. The interval between the major coronary event (myocardial infarction or coronary revascularization) and initial testing was at least 3 months and averaged 13.6 ± 4 months.

Treadmill exercise test and maximal O2 uptake capacity (VO2max). Maximal exercise testing was performed on a motor-driven treadmill according to the Bruce protocol24 with a repeat treadmill test 1 week later for measurement of VO2max by the following protocol: After 5 min of warm-up exercise that consisted of walking at 0 grade at a speed of 1.7 or 2.5 mph, patients began to exercise at the speed equivalent to the next to the last stage attained with the prior Bruce protocol with the grade set at either 5% or 10%, depending on the patients’ exercise capacity. From this point on the speed and grade were increased alternately every 2 min. The patients breathed through a Daniels valve, and expired gases were collected in neoprene meteorologic balloons at 60 or 30 sec consecutive intervals. Oxygen and CO2 were analyzed with a mass spectrometer (Perkin-Elmer MA1100). Expired volumes were measured with a Tissot spirometer. In 15 patients (14 without and one with angina) it was possible to obtain true VO2max, defined as attainment of the leveling-off criterion, and/or a respiratory exchange ratio of 1.15 or greater, signifying marked hyperventilation that usually occurs with VO2max.25 In the remaining 10 patients (nine with angina and one with LBBB), peak or symptom-limited O2 uptake (peak VO2) rather than VO2max was obtained.

Left ventricular function at rest and with exercise. Left ventricular performance was assessed by electrocardiographically gated cardiac blood pool imaging with erythrocytes labeled in vivo by intravenous injection of 7.7 mg of stannous pyrophosphate followed in 20 min by injection of 25 mCi of 99mTc. Images were obtained with a standard-field-of-view scintillation camera (Siemens LEM) equipped with a 0.64 cm thick NaI crystal and with a low-energy, medium-resolution, parallel-hole collimator. Images were obtained with the patients supine and with the scintillation camera positioned in the left anterior oblique (LAO) projection providing optimal separation of the ventricles (35 degrees). Caudal angulation (15 degrees) was used to maximally separate the left atrial and left ventricular images. Data were collected in the frame mode (32 frames per RR interval) in a 64 × 64 pixel matrix and processed off-line with a VAX 11/750 minicomputer equipped with a Lexidata display unit. The average number of background-subtracted counts per frame in the left ventricular region of interest at end-diastole at rest was 11,288 and that at peak supine bike exercise was 5377. Ejection fraction (EF) was calculated as: EF = (EDC – ESC) × 100/EDC, where EDC and ESC are the left ventricular end-diastolic and end-systolic counts, respectively, corrected for background activity. With this method, reproducibility is high, and left ventricular ejection fraction correlates well with results of contrast left ventriculography.26

The left ventricular end-diastolic volume (LVEDV) was calculated by the standard geometric area-length method27: V = 8 A3/3 π1, where V is volume, A is the area, and 1 is the long axis of the left ventricle. Spatial calibration factors for the X and Y axes of the digital images were obtained with the use of a phantom as described by Esser et al.28 The area and the long axis of the left ventricle were determined with an end-diastolic region of interest as previously described.29 The left ventricular end-systolic volume (LVESV) and stroke volume were derived from ejection fraction and LVEDV. The scintigraphic method used for volume measurements has been validated in our laboratory. Results correlate closely with those of contrast ventriculography (r = .97).

After images had been obtained in patients at rest, each performed a graded supine cycle exercise test with an electrically braked bicycle ergometer (Engineering Dynamics Corp.) that maintains a constant work rate over a wide range of pedaling frequencies. The pedaling rate was between 65 and 70 rpm. Work rates were increased by 25 W every 3 min until severe fatigue or angina developed. Images were obtained during the last 2 min of each stage of the exercise in the same modified LAO projection as that used for rest images. Heart rate was recorded every minute. Blood pressure was measured with a mercury sphygmomanometer at the second and third minutes of each stage of the exercise test. Peak heart rate and systolic blood pressure during supine cycle ergometer exercise are reported as the average of the values measured at the second and third minutes of the last stage of the exercise test.

The following parameters were used to evaluate left ventricular contractile function: (1) changes in ejection fraction as a function of systolic blood pressure (used as an estimate of afterload), (2) the systolic blood pressure–end-systolic volume relationship, and (3) the relationship between left ventricular work and end-diastolic volume (Frank-Starling mechanism). Regional left ventricular contraction abnormalities were evaluated subjectively by three investigators blinded to the patients’ category (training or control) and clinical status. Differences in opinion were resolved by consensus. Left ventricular ejection fraction and end-diastolic volume were measured by only one investigator blinded to the patients’ status. The intraobserver variabilities in the determinations of left ventricular ejection fraction and end-diastolic volume at rest were 0.1 ± 0.7% (r = .95) and 6 ± 3 ml (r = .88), and those at peak exercise were 1.7 ± 0.9% (r = .92) and 7 ± 3 ml (r = .92), respectively, in 10 randomly selected subjects.

Plasma lipids. Blood samples were obtained after subjects had fasted for 14 hr. Plasma cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels were assayed as previously described.30 The low-density lipoprotein (LDL) cholesterol level was calculated as previously reported.30 No specific diet recommendations were made. However, patients were encouraged to adhere to diets recommended by their personal physicians before referral to the exercise program.

Exercise program. The 12 month long exercise program used in this study has previously been described in detail.30 Briefly, patients were expected to exercise three times a week.
for the first 3 months and five times per week thereafter. The duration of exercise sessions was 40 to 45 min for the first 3 months and was increased progressively to 50 to 60 min of exercise exclusive of the warm-up and cool-down periods over the next 3 months. The training intensity ranged from 60% to 70% of the maximal attainable \( \text{VO}_2 \) for the first 3 months and was then gradually increased to 70% to 90% of maximal attainable \( \text{VO}_2 \) over a 6 month period. The intensity of training was assessed by measurement of heart rate and the relationship between heart rate and \( \text{VO}_2 \) and was verified periodically by collection of expired air and measurement of \( \text{VO}_2 \) during exercise.

All exercise sessions were supervised by a physician.

**Statistical analysis.** Student’s \( t \)-test for paired observations was used for comparison of the data before and after training. Chi-square analysis was performed when appropriate. Because LVEDV and LVESV conformed to log normal distributions, they were logarithmically transformed for the purposes of statistical analysis. However, the actual values are presented in the text, figures, and tables. Data are expressed as mean ± SE.

**Results**

**Baseline characteristics of patients.** There were no significant differences with respect to age (52 ± 2 vs 48 ± 2 years), \( \text{VO}_2 \text{max} \) (23 ± 0.6 vs 23 ± 1 ml/kg/min), or left ventricular ejection fraction (rest: 53 ± 3 vs 52 ± 3; exercise: 52 ± 3 vs 52 ± 3) between the exercising patients and those who did not exercise.

**Exercise training.** Exercise capacity and endurance improved markedly in response to the 12 months of training. For 10 patients the primary mode of training was running; during the last 3 months of the program they were running between 3.6 ± 0.3 to 5.2 ± 0.3 miles continuously per session, averaging 18.1 ± 1.6 miles/week. Thirteen patients were running 7.7 ± 1.3 miles/week in addition to performing exercise on a cycle ergometer for 20 to 30 min per day. One patient exercised predominantly on a cycle ergometer 60 min/day, 5 days/week during the last 3 months of the program. The peak training intensity in the last 3 months of the program was 89.4 ± 1.3% of maximal attainable \( \text{VO}_2 \) as documented by measurement of \( \text{VO}_2 \) during exercise sessions, and the attendance rate was 4.2 ± 0.1 sessions/week (minimum of 3 and maximum of 5).

**Maximal attainable \( \text{VO}_2 \) and symptoms.** Maximal attainable \( \text{VO}_2 \) was increased by 37% (\( p < .001 \)), from 23 ± 1 to 31.5 ± 1 ml/kg/min (1.85 ± 0.04 to 2.36 ± 0.08 l/min, \( p < .001 \)) for the entire group. True \( \text{VO}_2 \text{max} \) rose by 39%, from 23 ± 1 to 32 ± 1 ml/kg/min (\( p < .001 \)) in the 15 patients in whom it was attainable. Peak \( \text{VO}_2 \) increased from 24 ± 1 to 31 ± 2 ml/kg/min (\( p < .001 \)) in the remaining patients who did not attain true \( \text{VO}_2 \text{max} \). The exercise time during maximal treadmill exercise (Bruce protocol) was increased by 41% (367 ± 25 vs 517 ± 25 sec, \( p < .001 \)). Maximal work rate during supine cycle exercise increased from 97 ± 4 to 122 ± 3 W (\( p < .001 \)). In control subjects peak supine work rate was 97 ± 5 W initially and 93 ± 6 W a year later (\( p = NS \)).

Five of the 10 patients (Nos. 2, 5, 6, 8, and 15; table 1) who had effort angina became entirely asymptomatic, even during maximal treadmill exercise. In three of the remaining five patients (Nos. 13, 19, and 20; table 1), angina was considerably less in frequency and severity. Angina was unchanged in the other two patients (Nos. 14 and 18, table 1). There were no major complications attributable to exercise testing or training. Neither symptoms nor maximal exercise capacity changed in the 14 patients who did not participate in exercise training.

**Heart rate, blood pressure, and rate-pressure product.** Heart rate at rest decreased significantly from 64 ± 2 to 56 ± 2 beats/min (\( p < .001 \)) with training. Systolic and diastolic pressure at rest did not change. Submaximal heart rate, systolic and diastolic blood pressure, and rate-pressure product at the same work intensity (stage I of the Bruce protocol) were lower after training (figure 1).

The peak heart rate attained during supine exercise was 125 ± 4 before and 130 ± 3 beats/min after training (\( p < .01 \)), averaging 87% and 86% of the maximal heart rate during treadmill exercise initially and 1 year later, respectively. Systolic blood pressure (figure 2) and rate-pressure product (table 1) during supine cycle ergometer exercise were higher after 12 months of training. The rate-pressure product during maximal treadmill and supine cycle ergometer exercise was similar.

In the 14 patients who did not participate in exercise training, heart rate, blood pressure, and rate-pressure product during submaximal and maximal treadmill or supine cycle ergometer exercise did not change significantly over a 12 month interval (table 1).

**ST segment changes.** In the seven patients of the training group who were not on digoxin and for whom volumetric data and good quality electrocardiographic data were available, ST segment changes were significantly reduced during submaximal exercise, as documented by the change in the horizontal segments which were printed on the oscilloscope screen and for which the data are presented in figure 1.
After 12 months of training, left ventricular ejection fraction at the work rate equivalent to the peak work rate attained before training (97 ± 4 W) was significantly higher (51 ± 3% before vs 57 ± 3% after, n = 22, p < .005). Left ventricular ejection fraction during maximal supine exercise was also significantly higher, averaging 58 ± 3% after compared with 52 ± 3% before training (p < .001, n = 25; figure 3, table 1), despite a significantly higher rate-pressure product (table 1) and systolic blood pressure, a crude index of afterload (figure 4).

Left ventricular contractile function

Ejection fraction. Exercise training did not affect left ventricular ejection fraction at rest (table 1).

Left ventricular volumes. Volumetric data were available in 23 of the patients. LVEDV at rest was slightly but significantly increased from 148 ± 10 to 159 ± 10 ml (p < .025) after 12 months of training. At peak supine exercise, LVEDV was also significantly higher after training (148 ± 19 ml before vs 163 ± 10 ml after, p < .005). However, the changes in LVEDV from rest to exercise were negligible both in the trained and untrained states. In the 14 patients who did not exercise, LVEDV at rest (150 ± 14 vs 155 ± 13 ml) and at peak supine exercise (162 ± 18 vs 159 ± 15 ml) did not change over 12 months.

LVESV at rest was 75 ± 9 ml before and 78 ± 9 ml (p = NS) after training. Peak exercise values for LVESV were the same in the trained and untrained states (75 ± 9 vs 75 ± 11 ml). However, the directional changes in LVESV from rest to exercise were different, showing a decrease in LVESV after training (p < .05; figure 2). In the 14 patients who did not exercise, LVESV did not change significantly at rest (74 ± 10 vs 72 ± 9 ml) or with peak supine exercise (82 ± 13 vs 77 ± 11 ml).

Left ventricular contractile function

Ejection fraction. Exercise training did not affect left ventricular ejection fraction at rest (table 1). After 12 months of training, left ventricular ejection fraction at the work rate equivalent to the peak work rate attained before training (97 ± 4 W) was significantly higher (51 ± 3% before vs 57 ± 3% after, n = 22, p < .005). Left ventricular ejection fraction during maximal supine exercise was also significantly higher, averaging 58 ± 3% after compared with 52 ± 3% before training (p < .001, n = 25; figure 3, table 1), despite a significantly higher rate-pressure product (table 1) and systolic blood pressure, a crude index of afterload (figure 4).

Left ventricular volumes. Volumetric data were available in 23 of the patients. LVEDV at rest was slightly but significantly increased from 148 ± 10 to 159 ± 10 ml (p < .025) after 12 months of training. At peak supine exercise, LVEDV was also significantly higher after training (148 ± 19 ml before vs 163 ± 10 ml after, p < .005). However, the changes in LVEDV from rest to exercise were negligible both in the trained and untrained states. In the 14 patients who did not exercise, LVEDV at rest (150 ± 14 vs 155 ± 13 ml) and at peak supine exercise (162 ± 18 vs 159 ± 15 ml) did not change over 12 months.

LVESV at rest was 75 ± 9 ml before and 78 ± 9 ml (p = NS) after training. Peak exercise values for LVESV were the same in the trained and untrained states (75 ± 9 vs 75 ± 11 ml). However, the directional changes in LVESV from rest to exercise were different, showing a decrease in LVESV after training (p < .05; figure 2). In the 14 patients who did not exercise, LVESV did not change significantly at rest (74 ± 10 vs 72 ± 9 ml) or with peak supine exercise (82 ± 13 vs 77 ± 11 ml).
Systolic blood pressure–end-systolic volume relationship. LVESV decreased with exercise after but not before training (p < .05; figure 2). The systolic blood pressure attained during maximal exercise was significantly higher after training (171 ± 5 mm Hg before vs 189 ± 4 after, p < .001), shifting the pressure-volume relationship up and to the left (figure 2).

In the patients who did not participate in training, no significant changes in LVESV, systolic blood pressure, or the pressure-volume relationship occurred (figure 2).

Left ventricular stroke work–end-diastolic volume relationship (Frank-Starling mechanism). Left ventricular stroke work was higher at rest and during maximal exercise after (106 ± 6 g-m at rest and 159 ± 1 g-m with exercise) than before training (93 ± 5 g-m at rest and 125 ± 9 g-m with exercise, both p < .01). Furthermore, the change in left ventricular stroke work increased from 31 ± 7 g-m before to 50 ± 8 g-m after training (p < .005). LVEDV was significantly higher after training at rest and during maximal exercise. However, LVEDV did not increase from rest to exercise either in the trained or untrained subjects (0.1 ± 3 vs 4 ± 5 ml, p = NS). Therefore, the increase in left ventricular stroke work from rest to maximal exercise could not be attributed to an increase in preload.

In the 14 subjects who did not exercise, no significant changes in LVEDV or in left ventricular stroke work from rest to exercise occurred over 12 months.

Changes in regional left ventricular contraction abnormalities. Twenty-two of the 25 patients exhibited regional contraction abnormalities at rest before training. In four patients it was not possible to assess regional wall motion abnormalities during exercise because of the extensive contraction abnormalities present at rest. Exercise-induced contraction abnormalities were clearly detectable in 10 patients. Of these, eight showed improvement in exercise-induced wall motion disorders after training. In one patient the regional wall motion disorder became worse, and in another it remained unchanged. The improvements in regional wall motion abnormalities occurred despite a higher rate-pressure product (20.65 × 10³ ± 1.4 × 10³ vs 25.1 × 10³ ± 1.4 × 10³, p < .025), a larger LVEDV (126 ± 17 vs 135 ± 14 ml, p < .05), and a higher ejection fraction (55 ± 6% vs 61 ± 6%, p < .025) attained during maximal exercise.

Among the 14 patients who did not undergo training, an exercise-induced regional wall motion disorder was detected in five initially and in seven patients 12 months later. Of the five patients who had exercise-induced regional contraction disorders on the initial
radionuclide ventriculogram, four showed no change or deterioration of regional wall motion abnormalities, and one showed improvement in regional contraction abnormalities. The lack of improvement or deterioration of regional wall motion disorders was evident despite similar levels of rate-pressure product (23.55 × 10³ ± 1.4 × 10³ vs 23.56 × 10³ ± 1.8 × 10³, p = NS), LVEDV, and ejection fraction at peak exercise initially and a year later. The changes in regional wall motion disorders over a 12 month interval were significantly different between the training and nonexercising control groups (χ² = 8.305, p < .005).

Adaptive responses to training in patients with and without detectable myocardial ischemia. Maximal attainable VO₂ increased by 35% and 36% after 12 months of training in patients with and without evidence of myocardial ischemia, respectively. Ejection fraction did not change significantly in either subgroup with exercise before training (figure 5). After training, ejection fraction increased significantly during exercise in both subgroups (figure 5). Furthermore, peak exercise ejection fraction was significantly higher in the trained compared with the untrained states in both subgroups (figure 5). The higher ejection fraction was attained despite a significantly higher systolic blood pressure at peak exercise after training in both subgroups (figure 5).

In the subgroup with exercise-induced myocardial ischemia, the systolic blood pressure–LVESV relationship was shifted upward and to the left, with a smaller LVESV and higher systolic blood pressure, after 12 months of training. In patients with no apparent exercise-induced myocardial ischemia, the systolic blood pressure–end-systolic volume relationship was shifted only upward, with no significant change in LVESV but a significantly higher systolic blood pressure after training (figure 5). In the former subgroup, rate-pressure product at peak exercise increased from 19.87 × 10³ ± 4.26 × 10³ to 23.93 × 10³ ± 4.41 × 10³ (p < .001) after training. However, rate-pressure product did not change significantly at peak exercise (23.8 × 10³ ± 1.19 × 10³ vs 25.50 × 10³ ± 1.20 × 10³) in patients with no apparent myocardial ischemia. In both subgroups the changes in LVEDV from rest to exercise were insignificant.

Effect of training on plasma lipids. Training resulted in a significant weight loss from 80.8 ± 2 to 76.2 ± 2 kg (p < .001). No significant changes in weight occurred in the group that did not exercise.

Endurance exercise training had no significant effect on plasma total cholesterol (214 ± 10 vs 205 ± 9 mg/dl) or plasma triglycerides (174 ± 26 vs 142 ± 11 mg/dl). However, the HDL cholesterol level increased by 13% (39 ± 2 vs 44 ± 2 mg/dl, p < .005), improving the atherogenic index (total cholesterol to HDL cholesterol ratio) from 5.7 ± 0.3 to 4.7 ± 0.3 (p < .001). The LDL cholesterol level was 135 ± 8 mg/dl before and 126 ± 7 mg/dl after training (p = NS). This increase in the level of HDL cholesterol without a change in total cholesterol is not surprising because exercise was the only experimental intervention used.

Discussion

Our results provide evidence that endurance exercise training of progressively increasing intensity can improve left ventricular contractile function in some patients with coronary artery disease. This improvement appears to reflect a reduction in the severity of myocardial ischemia.

A rise in ejection fraction, as seen in healthy subjects during exercise, generally reflects an enhanced

![FIGURE 5. Adaptive responses to training in patients with and without detectable exercise-induced myocardial ischemia. A and C, Patients with exercise-induced ischemia exhibited a large increase in left ventricular ejection fraction (LVEF) at peak exercise after training (*p < .01 rest vs exercise; †p < .005 before vs after training at peak exercise), despite a higher peak exercise systolic blood pressure (SBP) (p < .005). The SBP–end-systolic volume (ESV) relationship was shifted upward and to the left with a decrease in LVESV (***p < .01) and a larger peak SBP (**p < .005). B and D, Similar changes in LVEF response were noted in patients without apparent provokable ischemia (*p < .01 rest vs exercise; †p < .05 before vs after training at peak exercise). However, the SBP–ESV relationship showed an increase in SBP (**p < .01) without a change in ESV. Data are mean ± SE.](http://circ.ahajournals.org/)

CIRCULATION
contractile state,31-33 reduced afterload,34,35 and/or a large increase in preload.35,36 Thus, a higher maximal exercise ejection fraction after training could be the result of either improved left ventricular contractile function secondary to a reduction in myocardial ischemia or of favorable changes in cardiac loading conditions. However, it is unlikely that an increase in preload contributed significantly to the higher exercise ejection fraction in our patients because the changes from rest to exercise in end-diastolic volume were negligible. Furthermore, a higher end-diastolic volume would be expected to raise the myocardial O₂ requirement37 and potentiate myocardial ischemia, which could in turn further impair left ventricular function. Although left ventricular wall stress cannot be measured reliably during exercise with the currently available noninvasive techniques in patients with coronary artery disease, it is unlikely that afterload was lower after training because peak exercise systolic blood pressure and LVEDV were significantly higher and end-systolic volume did not change. The upward and leftward shift in the systolic blood pressure–end-systolic volume relationship also suggests improvement in left ventricular contractile function38-40 even though peak systolic blood pressure may not reflect end-systolic pressure.

Improvement in left ventricular function in response to 12 months of training was evident both in patients with clear-cut evidence of exercise-induced myocardial ischemia and in those with no apparent provokable myocardial ischemia. However, the extent of the improvement in left ventricular function in response to training appeared to be more impressive in the patients with provokable ischemia than in those without it; this is evidenced by the difference in the systolic blood pressure–end-systolic volume relationship in the two subgroups, probably because the subjects in the latter group had larger myocardial scar than those in the former group. However, the presence of small areas of myocardial ischemia cannot be excluded in the subgroup in which ischemia was not detectable with our methodology. It is therefore likely that the primary mechanism for improvement in left ventricular function in the majority of our patients was a reduction in myocardial ischemia.

Spontaneous improvement in left ventricular contractile function over a 12 month interval is unlikely to account for our findings. Williams et al.41 did not observe any improvement in left ventricular function in a large number of patients who underwent exercise training of moderate intensity. Furthermore, the patients in the present study who did not exercise did not show improved left ventricular function 12 months later. Interventions designed to increase coronary blood flow, such as coronary artery bypass graft surgery, improve global and regional left ventricular function during maximal exercise by decreasing myocardial ischemia,42,43 making it possible to attain a higher myocardial VO₂. The myocardial O₂ requirement is influenced by heart rate, contractile state, and left ventricular wall tension.34 Left ventricular contractile function and regional wall motion abnormalities improved in our patients in response to training, despite attainment during maximal exercise of a higher heart rate. It is unlikely that left ventricular wall tension was lower after training because systolic blood pressure and end-diastolic volume were higher and end-systolic volume was unchanged at peak exercise. Furthermore, we have previously reported that patients who have adapted to the training program used in this study attain a higher concentration of plasma norepinephrine during maximal exercise,23 which, per se, raises myocardial O₂ demand.35 Thus, the improvement in left ventricular contractile function in our patients was not likely due to a lower myocardial oxygen requirement, but rather to an improvement in myocardial oxygenation. The present results extend our previous findings that intense exercise training can result in volume overload left ventricular hypertrophy in patients with coronary artery disease similar to that seen in healthy subjects.22 This physiologic hypertrophy is characterized by proportional increases in left ventricular radius and wall thickness, as reported previously.22

Several previous studies did not show improvement in left ventricular function9,10,41,44 or myocardial ischemia5,11,12 in response to exercise training in patients with coronary artery disease. These negative results most likely reflect an insufficient training stimulus rather than differences in the patient populations. The clinical status of our patients on entry to the study, in terms of exercise capacity and/or ejection fraction at rest, was similar to that of the patients in most other studies.4,5,9-12,41,44 The major obvious difference between our study and those of others is the nature of the training stimulus. The training intensity used in our study was high enough to induce a 37% increase in measured VO₂max. This was accomplished by progressively increasing the intensity, duration, and frequency of the exercise over the 12 month period rather than keeping the patients on a maintenance exercise regimen after 3 months of training.

The results of this study show that in addition to inducing adaptations that result in a lower heart rate and systolic blood pressure at the same submaximal
work rate, prolonged, high-intensity endurance exercise training can improve left ventricular systolic function during maximal exercise independent of cardiac loading conditions in some patients with coronary artery disease who can exercise regularly and intensely. This improvement is likely due to improved oxygenation of some of the underperfused regions of the myocardium.

References

Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease.
A A Ehsani, D R Biello, J Schultz, B E Sobel and J O Holloszy

Circulation. 1986;74:350-358
doi: 10.1161/01.CIR.74.2.350

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/74/2/350

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/