Effects of physical conditioning on left ventricular ejection fraction in patients with coronary artery disease

R. Sanders Williams, M.D., Ray A. McKinnis, Ph.D., Frederick R. Cobb, M.D., Michael B. Higinbotham, M.B., Andrew G. Wallace, M.D., R. Edward Coleman, M.D., and Robert M. Califf, M.D.

ABSTRACT To address the hypothesis that physical conditioning may improve left ventricular function in patients with coronary artery disease, we performed first-pass radionuclide ventriculography in 53 patients at rest and during upright bicycle exercise before and after 6 to 12 months of exercise training. The peak bicycle workload achieved before the onset of fatigue, dyspnea, or angina increased by an average of 22% (p = .0001) after training, and mean heart rate at a workload equal to the pretraining maximum workload was decreased by 10 beats/min after training (p = .0002). Of 21 subjects with angina or exertional ST segment depression before training, 15 (71%) were able to exercise to the same workload without these manifestations of ischemia after training. Whereas neither mean resting left ventricular ejection fraction (LVEF) nor LVEF at peak exertion was significantly altered, mean LVEF at the pretraining maximum workload was increased from 0.50 to 0.54 (p = .002) after training. There was a significant correlation between the magnitude of training bradycardia and the increment in LVEF at the pretraining maximum workload (p = .009). We conclude that the relative bradycardia at comparable exercise workloads produced by exercise conditioning is associated with improvements in left ventricular performance as assessed by the LVEF. This observation is compatible with the hypothesis that training bradycardia in conditioned subjects with ischemic heart disease is associated with lower myocardial oxygen demand and lesser degrees of ischemia at comparable workloads. However, training effects on ventricular afterload or on intrinsic contractile performance of the heart cannot be excluded.


EXERCISE TRAINING in patients with ischemic heart disease produces two major sequelae — increased work capacity and a relative bradycardia at any given workload — that are qualitatively similar to the changes produced in normal subjects. This observation has provided at least part of the rationale for the currently prevalent application of exercise training programs as therapy for patients with angina pectoris or for those recovering from myocardial infarction.

Since under most circumstances heart rate is an important determinant of myocardial oxygen demand, the relative bradycardia produced by exercise training would be expected to produce a more favorable balance between oxygen supply and demand in the myo-
these effects in man, and recent animal studies have failed to confirm the earlier reports of training-induced augmentation of coronary collateralization. Likewise, several recent studies in which radionuclide ventriculography has been used to assess the cardiovascular effects of exercise training in small groups of coronary patients have produced somewhat disparate results. Our current research, incorporating a sample size exceeding the combined total of those in the previous studies addressing this issue, was designed to resolve the controversy generated by these previous investigations and to provide a more rigorous test of the hypothesis that exercise training improves left ventricular ejection fraction (LVEF) in patients with coronary artery disease.

Methods

Subjects and study design. The study population consisted of 53 patients with coronary artery disease, as determined either by a documented prior myocardial infarction or by coronary arteriographic results demonstrating a 75% or greater stenosis in at least one major vessel. The subjects ranged in age from 36 to 68 (median 52) years and 91% were men. Forty-two subjects had experienced a prior myocardial infarction, but no subject entered the study earlier than 8 weeks after he had had an infarction.

The study population was heterogeneous in terms of exercise capacity and ventricular function before training: the peak bicycle workload attained ranged from 300 to 1200 (median 750) kilopond-meters (kpm)/min and resting LVEF ranged from 0.14 to 0.86 (median 0.56). Twenty-five subjects had a history of typical angina pectoris, and 21 subjects experienced typical angina and/or had electrocardiographic (ECG) changes indicative of ischemia (0.1 mV of flat or downsloping ST depression) during bicycle exercise.

Coronary arteriographic data were available for 18 patients (34%): one subject had single-vessel disease (≥75% stenosis), seven had double-vessel disease, and 10 had triple-vessel disease. Two subjects had 75% stenosis of their left main coronary arteries. Coronary artery bypass grafting had been performed before entry into the study in nine of these 18 subjects, but postoperative coronary angiograms were not obtained. The 53 subjects represent a subset of 513 consecutive patients with coronary artery disease referred to our cardiac rehabilitation program. These 53 gave informed consent for and underwent two technically adequate radionuclide angiographic studies separated by a 6 to 12 month period. During this period the subjects pursued the exercise training regimen described below. The study population did not differ significantly from the overall population with respect to sex distribution or treadmill work capacity, although the study participants were marginally younger (52 vs 55 years; p = .03). Likewise, resting LVEF in the study population was not significantly different from that observed in the 224 other patients in whom data on baseline resting ventricular function were available as the results of isotope or contrast ventriculographic tests (LVEF 0.54 vs 0.52; p = .50).

Treadmill exercise test. Before and after 6 to 12 months of exercise conditioning, subjects underwent symptom-limited graded exercise testing on a treadmill (Quinton Model 18-54) with continuous electrocardiographic monitoring.

Radionuclide ventriculography. Subjects underwent radionuclide angiographic examination by the first-pass technique at rest and during upright bicycle exercise as described in detail in previous publications from our laboratory. Briefly, 10 mCi of 99mTc-pertechnetate was injected as a single bolus into a 20-gauge Teflon catheter that had been previously introduced into an external jugular vein. Counts were acquired at 25 msec intervals in the anterior projection with the Baird Atomic System Seventy-Seven, which includes a multicroystal camera and a 2.54 cm parallel-hole collimator. Scintigraphic data were stored on magnetic discs and, after correction for background activity and electronic dead time, data from 3 to 6 individual beats were combined to produce an average or representative cycle. Ejection fraction was calculated as: (end-diastolic counts − end-systolic counts)/end-diastolic counts. A computerized edge-detection program was used to outline the end-diastolic perimeter of the left ventricular image, and end-diastolic volume was calculated by the area-length method of Sandler and Dodge.

End-systolic volume was derived as the product of end-diastolic volume and (1 − ejection fraction). These methods have been validated in our laboratory by comparison with results of contrast ventriculography and have been shown to be highly reproducible.

For the pretraining study ventriculographic data were acquired at rest and during exercise at the maximum workload tolerated before fatigue or progressive angina mandated the termination of the study. For the posttraining study ventriculographic data were acquired at rest, at a workload equal to the maximum level achieved on the pretraining study (a submaximal workload for most subjects after training), and at the onset of fatigue or angina. Subjects were instructed to exercise to a level of fatigue or angina similar to that in the pretraining study. The reproducibility of serial radionuclide studies in the absence of a specific intervention was assessed in a separate population of 43 men with angiographically documented coronary artery disease who agreed to return for a repeat study 6 to 34 (mean 19) months after initial, clinically indicated radionuclide angiograms had been obtained. These subjects were studied by methods identical to those used in our exercise training group, including withdrawal from cardiac medication as described below, but received no specific instructions regarding their exercise habits in the period between their two radionuclide studies. At the time of their initial study, these patients were similar to our exercise group in terms of age (30 to 69 years; mean 49), anatomic severity of coronary heart disease (16 with one-vessel disease, 16 with two-vessel disease, and 11 with three-vessel disease), maximum exercise heart rate (137 ± 20 beats/min), and peak bicycle workload attained (692 ± 186 kpm/min). About half (19 of 43) of these subjects had experienced prior myocardial infarction, but none was studied sooner than 12 weeks from the date of infarction. These subjects demonstrated no significant changes during serial testing with respect to mean values for resting LVEF (0.62 ± 0.10 vs 0.63 ± 0.10) or for LVEF at peak effort (0.58 ± 0.15 vs 0.60 ± 0.13).

Training program. Subjects exercised three to five times weekly for 30 to 60 min, using a combination of stationary bicycle ergometry, stair climbing, walking, and jogging. The amount of exertion was adjusted to maintain the exercising heart rate at between 65% and 85% of the increment between the resting and maximum heart rates plus the resting heart rate (as observed during the pretraining treadmill exercise test). The study population included local residents who participated in a medically supervised exercise program for the entire duration of the study, as well as subjects from distant communities who received instructions during 2 to 6 weeks of participation in the supervised program, but who continued training without direct medical supervision until they returned for follow-up testing.

Medications. Drugs were prescribed as clinically indicated during the training program, but were withdrawn for treadmill exercise.
and bicycle exercise testing. β-Adrenergic–antagonist therapy was tapered beginning 7 to 10 days before exercise testing, and was stopped entirely for 48 hr. All other drugs were withheld for a minimum of 12 hr before exercise testing. Before the training program subjects receiving β-adrenergic antagonists were also retested while on their usual dosage; exercise was prescribed on the basis of a heart rate range calculated from data from the medicated, as opposed to the unmedicated, treadmill exercise tests. The validity of this approach for ensuring a similar percentage of maximum oxygen consumption during the training stimulus has been demonstrated.17

Data analysis. Postconditioning values for all variables were compared with pretraining values by the nonparametric Wilcoxon signed-rank rest for paired variables. Associations between continuous variables were assessed by Spearman’s rho, a nonparametric correlation index.

Results

The conditioning program was associated with increments in work capacity, as assessed during either treadmill testing or by bicycle ergometry, as well as with decrements in heart rate at a constant exercise workload equal to the pretraining maximum bicycle workload (table 1). Of 21 subjects who experienced typical angina and/or ischemic ECG changes indicative of ischemia at peak effort during bicycle exercise before training, 15 (71%) were able to exercise to the pretraining maximum workload without angina or significant ECG changes after training. In contrast, only three of 32 subjects (9%) without angina or ECG changes before training had either one at the pretraining maximum bicycle workload after training.

Concomitant with these changes, which constitute well-described adaptations to exercise training, we observed differences in LVEF during exercise after the conditioning program (table 2 and figure 1). LVEF was unchanged at rest, but was significantly higher during exercise at the pretraining maximum workload after training (figure 1 and table 2). The augmentation of LVEF at the pretraining maximum workload correlated significantly with the magnitude of training bradycardia (figure 2), but appeared to be unrelated to the degree of impairment of resting left ventricular function before training (figure 3). There was a significant correlation between the short-term change in LVEF from rest to exercise on the pretraining study with the improvement in LVEF at the pretraining maximum workload (figure 4), suggesting that patients initially exhibiting higher degrees of exertional ischemia demonstrated the largest improvements in this variable after training.

When exercise was continued to a symptom-limited end point, which required considerably more work and was achieved at a slightly higher heart rate after training (table 1), mean LVEF fell to a value statistically indistinguishable from the pretraining level. Of 21 subjects with angina or significant ST-segment changes during bicycle exercise before training, five (24%) did not develop these manifestations of ischemia even during maximum exercise after training, despite the fact that they achieved a higher heart rate and workload. On the other hand, four of 32 subjects

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Effects of exercise training on work capacity and heart rate (mean ± SD)</th>
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<tbody>
<tr>
<td></td>
<td>Before training</td>
</tr>
<tr>
<td>Peak bicycle workload (kpm/min)</td>
<td>747 ± 202</td>
</tr>
<tr>
<td>Total work performed on bicycle (kpm × 10^3)</td>
<td>28 ± 13</td>
</tr>
<tr>
<td>METS (treadmill)</td>
<td>7.4 ± 1.9</td>
</tr>
<tr>
<td>Heart rate at maximum pretraining bicycle workload (bpm)</td>
<td>139 ± 16</td>
</tr>
<tr>
<td>Heart rate at peak effort during bicycle exercise (bpm)</td>
<td>139 ± 16</td>
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</tbody>
</table>

METS = multiples of resting oxygen consumption estimated from peak treadmill speed and grade.

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Effects of exercise training on LVEF (mean ± SD)</th>
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<tbody>
<tr>
<td></td>
<td>Before training</td>
</tr>
<tr>
<td>LVEF at rest</td>
<td>0.52 ± 0.17</td>
</tr>
<tr>
<td>LVEF at maximum pretraining workload</td>
<td>0.50 ± 0.17</td>
</tr>
<tr>
<td>LVEF at peak effort</td>
<td>0.50 ± 0.17</td>
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FIGURE 1. Cumulative frequency distribution of LVEF at an exercise workload equal to the pretraining maximum workload before (solid line) and after (dashed line) exercise training. The approximately parallel shift of the posttraining from the pretraining distribution plot indicates that increases in LVEF occurred irrespective of the pretraining values for this variable.
FIGURE 2. Correlation between the change in heart rate and the change in LVEF at the pretraining maximum (fixed) workload induced by the training program. Closed circles represent data from subjects without angina and open circles those from subjects with angina.

Left ventricular end-diastolic volume was unchanged after training at rest (156 ± 51 vs 156 ± 63 ml), during exercise at a constant workload (188 ± 59 vs 187 ± 70 ml), and at peak effort (188 ± 59 vs 194 ± 82 ml). End-systolic volume was unaltered at rest (74 ± 22 vs 71 ± 25) or at peak effort (94 ± 28 vs 93 ± 37). However, end-systolic volume was significantly reduced during exercise at an equivalent workload after training (94 ± 28 vs 85 ± 30; p = .006).

Because of the heterogeneous nature of our study population the possibility existed that physiologically significant effects of training occurring only within certain subgroups might be obscured by an analysis of data from the entire group. To address this possibility, we performed a series of subgroup analyses, stratifying our patients on the basis of the following clinical variables: history of angina (yes vs no), angina and/or ischemic ECG changes during bicycle exercise (yes vs no), short-term fall in LVEF from rest to exercise of greater than 0.05 (yes vs no), duration of training (< 9 vs > 9 months), administration of β-adrenergic antagonists during the entire training period (yes vs no), number of diseased vessels (not known vs one vs two vs three), prior coronary artery bypass graft (yes/no), location of myocardial infarction (anterior vs inferior vs subendocardial/indeterminate vs none), and major site of training (home vs center). The results from such subgroup analyses must be interpreted with extreme caution.
caution because of the increased likelihood of obtaining spurious statistically significant differences due to the multiple comparisons involved and also because of the large type II statistical error associated with the smaller sample sizes available within the subgroups. These analyses should therefore not be regarded as rigorous hypothesis testing. The results of the analyses, however, may be useful in generating new hypotheses or to aid in the design of future studies. Across all of the 24 subgroups the mean reduction in heart rate at a standard bicycle workload after training ranged from 2 to 13 beats/min and the mean increment in peak bicycle workload attained ranged from 95 to 205 kpm/min. Both of these variables tended to show greater changes after training in subjects pursuing a longer duration of training (>9 months vs <9 months) and in those with inferior or subendocardial/indeterminate myocardial infarction than in those with anterior myocardial infarction, but otherwise no major differences among the subgroups were discernible.

Regarding the ejection fraction measurements, resting LVEF after training varied from −0.01 to +0.04 and was statistically different from zero in only three subgroups: those with no prior coronary artery bypass grafting, no cardiac catheterization, or short-term fall in LVEF greater than 0.05. LVEF at the pretraining maximum workload was increased in all of the subgroups, ranging from +0.02 to +0.06. This was a statistically significant increase in 14 of the 20 subgroups containing more than 10 subjects, but there were no convincing differences among the subgroups. LVEF at peak effort varied, ranging from −0.02 to +0.03, and achieved borderline statistical significance only in the subgroup of subjects without a prior history of angina (+0.03; n = 26, p = .03) and in those without angina or ECG changes on their baseline bicycle exercise tests (+0.02; n = 29, p = .05). In 30 subjects in whom there was evidence of exertional ischemia, as determined by any one of three criteria (typical angina, ST segment depression, or a short-term fall of LVEF from rest to exercise of 0.05 or more during bicycle exercise), LVEF at peak effort showed no change after training. However, LVEF at peak effort was increased after training (+0.03; p = .04) in the 23 subjects in whom there was no evidence of exertional ischemia.

**Discussion**

Cardiovascular adaptations to exercise training in patients with coronary heart disease, including increased functional work capacity and decreased heart rates at rest and at any given exercise workload, have been reproducibly described in numerous studies over the last two decades. However, only a limited number of recent studies have investigated the effects of exercise training on left ventricular function during exercise in such subjects, and they have yielded somewhat disparate results.

Verani et al.12 studied 16 patients who had undergone 3 months of exercise conditioning and serial radionuclide scans of their left ventricles by the first-pass technique during upright bicycle exercise. In conjunction with a mean improvement in estimated maximal oxygen consumption of 17%, these investigators observed a significant increase in resting LVEF, but no change in LVEF at peak exertion. No studies of submaximal exercise were performed.

From our own laboratory11 there has been a report of results of first-pass radionuclide ventriculography during upright bicycle exercise in 11 subjects who had experienced myocardial infarction 2 to 12 months before entry into a structured exercise program. Although 6 months of physical conditioning in this population was associated with a 26% increment in exercise duration on a standard bicycle protocol and a mean reduction in heart rate at a standard submaximal bicycle workload of 9 beats/min, we observed no significant differences in LVEF at rest, during submaximal work, or at peak exertion.

Jensen et al.10 studied 19 patients during supine bicycle exercise with multigated equilibrium radionuclide angiography before and after a 3 to 9 month conditioning program that was sufficient to produce a fall in mean heart rate of 10 beats/min during exercise at a standard workload. They observed no change in resting LVEF or in LVEF at peak exertion, but noted a significantly higher LVEF at a standard workload (0.59 vs 0.55) after exercise conditioning, results that are similar to our current findings.

Our current results provide an explanation for the apparent discrepancies in the results of these earlier studies, and extend the conclusions that may be drawn regarding the effects of exercise training on ventricular performance in coronary artery disease. First, our data illustrate a clear association between reduced heart rate and increased LVEF during submaximal work after exercise training, both by the significant changes in mean values (tables 1 and 2), and by the significant correlation between the training-induced changes in these variables (figure 2). However, the magnitude of the change in LVEF is small, and could be missed due to a type II statistical error in studies in which smaller numbers of subjects are included. Second, in contrast to the studies performed by Jensen et al.,10 our radionu-
clude studies were performed in patients exercising in the upright position, a form of exertion more directly related to patients’ daily activities.

It is evident that the group of subjects included in this study may differ from the general population of those with coronary artery disease by virtue of several actual or potential selection factors, including (1) pre-screening by referring physicians in favor of motivated subjects or of subjects thought to be poor candidates for surgical revascularization procedures, (2) exclusion of subjects with unstable angina New York Heart Association class IV angina, or congestive heart failure, (3) the requirement for medication withdrawal, which excluded patients whose conditions were thought to be potentially unstable by the managing physician, and (4) self-selection of those subjects who continued on their exercise programs for the duration of the study and returned for follow-up testing. Despite these potential selection factors, our study population included individuals with a broad range of clinical characteristics at baseline. In terms of functional capacity, ventricular function, and anatomic severity of disease, our study population appeared to be representative of a general population of coronary patients that might be encountered in clinical practice.

Regarding the question of whether the presence of exertional myocardial ischemia may modify physiologic responses to exercise training, our data indicate that the presence of exertional ischemia does not preclude training-induced increments in exercise capacity or training-induced decrements in heart rate at a fixed exercise workload. If we regard a fall in LVEF during symptom-limited exercise (as compared with the resting value) as indicative of exertional myocardial ischemia in this population, then our data demonstrate that the largest increments in LVEF during submaximal effort after training occurred in subjects with exertional ischemia (figure 4). Regarding LVEF at peak exercise, our data suggest the possibility that coronary patients without exertional ischemia are more likely to demonstrate changes in this parameter of ventricular performance than subjects with exertional ischemia. Whereas mean LVEF at peak effort was unchanged after training in subjects with a clinical history of angina, typical angina, and/or ECG changes during bicycle exercise and in subjects with a short-term fall in LVEF from rest to exercise of 0.05 or more, subjects without any of these manifestations of myocardial ischemia demonstrated a slight but significant increase in LVEF (+0.02 to +0.03) at peak effort after training. Because this latter conclusion is based solely on the results of subgroup analysis, it should be regarded as tentative until it can be confirmed by subsequent investigations.

In an analogous fashion to the changes observed in normal subjects undergoing intense training, some of our subjects with coronary artery disease developed an increased LVEF and stroke volume at maximal exertion. However, such adaptations do not appear to be necessary for improvements in maximum work capacity to occur. Because we observed no changes in mean values for LVEF or left ventricular end-diastolic or end-systolic volume at peak exertion after training, it appears that our subjects tended to rely more on enhanced oxygen extraction by exercising skeletal muscle, a more favorable redistribution of cardiac output to exercising skeletal muscle, or increases in maximal heart rate than on increases in stroke volume as the physiologic basis for increased work capacity after training. Our patients did exercise to a significantly higher maximum heart rate after training and, despite this higher heart rate, maintained their peak exertional LVEFs at least at the pretraining level. Whereas these data do not exclude the possibility of marginal improvements in myocardial perfusion or in mechanical performance of the heart under ischemic conditions in physically conditioned patients with coronary disease, they suggest that dramatic improvements in these variables are not common sequela of the type of training pursued by our patients. Whether different effects might be observed with more intense training over a longer time period remains to be determined.

In summary, exercise training in a heterogeneous population of patients with coronary artery disease was associated with enhanced LVEF during exercise at a constant workload. Enhanced LVEF at a workload equal to the pretraining maximum workload after exercise conditioning may be attributable to a more favorable balance between myocardial oxygen demand and supply, mediated by the lower heart rate (and subsequently lower myocardial oxygen demand) at comparable exercise workloads after training, but the favorable changes in the loading conditions of the heart or changes in intrinsic myocardial contractility may also contribute to this effect of training.

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