Increase in myocardial oxygen consumption indexes by exercise training at onset of ischemia in patients with coronary artery disease

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ABSTRACT It has been unclear whether exercise training of patients with coronary artery disease increases the level of myocardial oxygen consumption, as indicated by heart rate and double product of heart rate and systolic blood pressure, at which electrocardiographic evidence of myocardial ischemia develops. To assess this question we evaluated the experience of 10 patients with coronary artery disease who underwent a modest-level exercise training program for 6 months. All of these subjects had achieved a training effect, had developed electrocardiographic evidence of ischemia during initial exercise testing, had not increased the amount of cardiac medication taken, and had not been taking digoxin. After completion of the training period, the mean heart rate at which electrocardiographic evidence of ischemia developed increased from 107 ± 19 to 119 ± 23 beats/min (p < .05) and the mean double product increased from 166 ± 18 to 209 ± 51 × 10² mm Hg × beats/min (p < .05). Eight of the 10 patients demonstrated an increase in heart rate at onset of ischemia (p < .02), and seven of the eight in whom double product could be assessed manifested an increase in this parameter at onset of ischemia (p < .05). Thus the rate of myocardial oxygen consumption at which myocardial ischemia develops, as indirectly assessed by heart rate and double product, can be favorably altered by 6 months of moderate-level exercise training.


AEROBIC exercise training is an established modality of treatment for patients with a variety of manifestations of coronary artery disease. The well-documented benefits of training include increased maximal functional capacity and decreased heart rate response to submaximal workloads. Because heart rate is a major determinant of myocardial oxygen consumption, training of patients with coronary artery disease often allows them to perform at a greater activity level before the onset of ischemia. Unresolved is the important question of whether there is an actual increase in the "ischemic threshold" of heart rate or double product (of heart rate × systolic blood pressure) at which ischemia appears. Evidence bearing on this question has been conflicting and sparse. To explore this issue further, we have evaluated the influence of exercise training on the onset of electrocardiographic evidence of exercise-induced myocardial ischemia in patients with coronary artery disease in our cardiac rehabilitation program.

Methods All patients who had participated in the community-based University of California, Davis, Medical Center Cardiac Rehabilitation Program between January 1979 and January 1984 were considered for inclusion in this study. Exclusion criteria were failure to complete 6 months of participation in the program or to achieve a training effect during this time, absence of ischemic ST segment changes on initial exercise test electrocardiogram, an increase in cardiac medication during the evaluated period of training, or use of digoxin during testing. Patients had been admitted to the Cardiac Rehabilitation Program because of previous myocardial infarction or coronary artery bypass surgery, angiographically documented coronary disease, or classic angina pectoris.

Each patient underwent exercise electrocardiography upon initial entry into the program and had approximately 6 months (mean 29 weeks, range 23 to 36 weeks) of participation in the training program. This testing was performed with a treadmill and a standard 12-lead electrocardiographic recording system. A Balke protocol was used that had been modified to allow flexibility in accommodating widely varying patient exercise capacities. Initial treadmill speed was individualized between 1.7 and 2.6 mph (46 and 70 meters/min). initial slope was 0 degrees. These levels were increased every 2 min depending on individual response. Functional capacity was taken at the highest symptom-limited workload attained and expressed in terms of...
of estimated oxygen consumption. For convenience, these values were converted to mets (one met = 3.5 cc oxygen consumption/kg/min). Electrocardiographic recordings included a standard 12-lead electrocardiogram with the patient sitting and standing before exercise, a three-lead electrocardiogram at each minute of exercise, a 12-lead electrocardiogram immediately upon cessation of exercise, and a three-lead electrocardiogram at each minute thereafter during the recovery phase. At each of these times, blood pressure was measured by use of an arm sphygmomanometer and auscultation. Heart rate was determined by averaging the directly measured R-R intervals of the first 10 beats of each recording (unless the heart rate was sufficiently slow that fewer beats had been recorded, in which case all beats recorded were measured).

Based on the initial exercise test, an individual exercise prescription was developed for each patient. This used a target heart rate equal to that produced by a workload of approximately 70% of the patient's maximal capacity determined by the initial test. This heart rate was to be maintained for at least 20 min during each exercise session, with sessions occurring three times weekly. Exercise involved walking, jogging, running, stationary bicycle riding, or rowing as appropriate for each patient.

The onset of electrocardiographically demonstrated myocardial ischemia was considered to be at the time (1 min increments) of first manifestation of at least 1.0 mm of ST segment depression at 80 msec after the J point. If resting ST segment depression was present, an ischemic response was considered an additional 1 mm of ST segment depression. Evaluation of this criterion was made by blinded independent review of the exercise electrocardiograms by two experienced cardiologists. Discrepancies of interpretation during these independent reviews were resolved by consensus.

Student's t test for paired data was used to assess the statistical significance of differences between pretraining and postraining functional capacities, and heart rates and double products at onset of electrocardiographic ischemia. Assessment of the statistical significance of the proportion of patients who had increased heart rate or double product at onset of ischemia was made by the chi-square method with Yates' correction for continuity. Differences were considered significant at p < .05.

Results

Patients. Of the 78 patients who had participated in the exercise rehabilitation program, 10 remained for assessment of heart rate at onset of ischemia after application of the exclusion criteria. (Two of the patients in this group could not be evaluated for double product at ischemic threshold because of inadequate blood pressure data.) Of the original 78 patients, two failed to demonstrate a training effect and 49 did not manifest ST segment evidence of ischemia on initial testing. Three of those remaining elected to complete only 3 months of the program; eight of those still available for analysis were taking digoxin; five of the remaining patients had increased intake of cardiac medications during the training interval; and the initial exercise electrocardiogram of one patient was uninterpretable.

Of the 10 patients remaining for evaluation, two had experienced prior myocardial infarction, three had undergone coronary artery bypass surgery, eight had catheterization-documented coronary artery disease, and four had classic angina. Two of these patients had angina during both pretraining and postraining exercise testing and one during only the latter testing; one failed to have angina during either exercise test. Of the eight who had undergone coronary angiography, five were found to have one-vessel disease, one had two-vessel disease, and two had three-vessel disease. A ninth patient experienced sudden death after completion of the 6 month training and was found at autopsy to have severe left main coronary artery disease. Nine of the 10 patients were men. The mean age was 56.2 years (range 37 to 71).

Functional capacity. The mean increase in functional capacity for the 10 patients was 1.6 mets. At initial evaluation the group mean was 7.2 ± 1.6 mets; this increased at the 6 month evaluation to 8.8 ± 1.9 mets, representing a significant increase at p < .001. The range of increase in functional capacity was 0.5 to 2.8 mets.

Ischemic threshold. At initial testing, the first electrocardiographic evidence of ischemia developed at a mean of 107 ± 19 beats/min (range 79 to 143) and 166 ± 18 × 10² mm Hg × beats/min (range 145 to 195). At the 6 month testing, these parameters had increased to 119 ± 23 beats/min (range 91 to 149) (figure 1) and 209 ± 51 × 10² mm Hg × beats/min (range 145 to

![FIGURE 1](http://circ.ahajournals.org/)

**FIGURE 1.** Heart rates at which electrocardiographic evidence of myocardial ischemia developed before and after exercise training of patients with coronary artery disease. Horizontal bars indicate the group means at each testing period.
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305) (figure 2). These increases both were significant at the p < .05 level. The range of changes in these parameters was −10 to +40 beats/min and −7 to +143 × 10^2 mm Hg × beats/min, respectively. During this interval, eight of the 10 patients demonstrated an increase in heart rate at which electrocardiographic ischemic evidence developed, one exhibited a decrease, and one was unchanged. By chi-square analysis, this demonstrated a likelihood of a real effect at the p < .02 level. The double product increased in seven patients and decreased in one. Similar analysis demonstrated this to be significant at the p < .05 level.

Angina. Both patients with angina on initial exercise testing had an increase in the heart rate at which angina occurred on the second test, one from 82 to 100 beats/min and the second from 84 to 118 beats/min.

Discussion

Aerobic exercise training is now accepted as a useful component of comprehensive management of coronary artery disease.1−2 The benefits of training include an augmented functional capacity and lower heart rates or double products (of heart rate × systolic blood pressure) at submaximal workloads.1−2 Additionally, psychological disability may be lessened, particularly in a peer-oriented group program.11 These improvements are routinely achievable, except in patients with severe disability or lack of motivation, despite the use of cardiac medication, including β-blockers.12 However, the issue of whether exercise training improves longevity in coronary patients remains unresolved,13 and existing evidence does not support the hypothesis that exercise therapy has an effect on ventricular ectopy.14

With the achievement by exercise training of lowered heart rates and double products at submaximal workloads, the myocardial oxygen consumption required to achieve an external workload is decreased. Thus a task that produced angina or other manifestation of myocardial ischemia before training may no longer do so after training. The mechanisms producing this benefit have been extensively investigated15,16 and include improved efficiency of peripheral musculature by increased mitochondrial mass and oxygen extraction17 and decreased circulating catecholamines at submaximal workloads.18 There is no evidence of improvement in myocardial collateral circulation.19,20 Likewise, improved left ventricular function, as evaluated by such parameters as ejection fraction, has not consistently improved with training in patients with coronary disease.19,22

Thus it might be expected that the level of cardiac work, measured by heart rate or double product, at onset of myocardial ischemia would remain unchanged after training, even though this level would be reached at a higher external workload. Some investigations of this question have used angina as the criterion of onset of ischemia4−7,9; often,1,6,7,9 but not uniformly,5 determinants of cardiac work at onset of angina have been noted to increase with training. Confusing the meaning of these findings has been the observation that after training the perception of angina onset tends to occur at a greater degree of ST segment depression than before training.5,7 It is not known whether the divergence of these two criteria of ischemia, angina and ST segment depression, is due to real but unexplained physiologic alteration or to a decreased psychological awareness of angina. Data are scarce with ST segment alteration used as objective evidence of ischemia in evaluating possible alteration of ischemic threshold by training. Detry and Bruce7 found no change in the heart rate or double product producing progressive degrees of ST depression after 3 months of training. Although the details of intensity of training were not specified, it was implied that training was at a moderate level. More recently, Ehsani et al.,9 hypothesizing that the former study failed to demonstrate an improvement in ischemic threshold because of inadequate duration and intensity of training, evaluated
patients who had undergone 12 months of relatively intense training. They found that the double product at which 0.1 mV ST depression first appeared was 22% higher after training than before training and that the heart rate increased 16%. Moreover, these parameters increased in each of their 10 patients.

Our study extends the information provided by the last two reports. As did those investigators, we used ST segment alteration rather than angina as the criterion of development of myocardial ischemia. The training period of 6 months in this investigation was between those of one-fourth and 1 year reported on in the previous studies. The training protocol used by our patients was of moderate intensity and likely more similar to that used by Detry and Bruce than to the more intense one used by Ehsani et al. We found that this 6 month moderate-intensity training program increased the heart rate and double product of heart rate \( \times \) systolic blood pressure at which ST segment depression consistent with myocardial ischemia developed. This was true not only for the group mean, but additionally for almost all of the individual patients (eight of 10 for heart rate, and seven of eight for double product).

Although the number of patients in whom onset of angina could be used as a marker of ischemic threshold was too small for analysis (n = 2), it is of interest that the heart rate at onset of angina increased notably in both.

Assuming that onset of ST segment depression indicates onset of myocardial ischemia, our findings support the concept that exercise training can favorably influence the oxygen supply-demand relationship of cardiac muscle during exercise. Additionally, our results suggest that the stimulus for this benefit need not be as stringent as that used by Ehsani et al. Although 3 months of training at a moderate workload is typically sufficient to induce the classic lowering of heart rate and double product at submaximal workloads and increase the maximum achievable workload, 6 months of training at this same moderate exercise level was adequate in our experience to raise the threshold of heart rate and double product at which ischemic electrocardiographic changes became manifest in those who had such changes. This is a noteworthy finding, since the study of Detry and Bruce was not suggestive of a beneficial alteration in the ischemic threshold occurring with training, and the more recent report of Ehsani et al. although demonstrating this benefit, implied the necessity of an arduous training regimen for its achievement. By contrast, in our experience elevation of the ischemic threshold can be achieved within the context of a routine cardiac rehabilitation program.

The explanation for this apparent elevation by exercise training of the threshold of cardiac work required to induce myocardial ischemia is not readily apparent. Although not supported by existing evidence, an augmentation of myocardial oxygen supply must be considered, since heart rate and double product correlate reasonably well with myocardial oxygen consumption. However, other determinants of myocardial oxygen consumption not encompassed by the heart rate or the double product (contractility, ventricular volume) may be influenced by training, and the heart rate and double product are thus not without limitations as indicators of myocardial oxygen utilization. Thus cardiac oxygen requirements may fall because of the effects of training on determinants of cardiac oxygen requirements other than the heart rate and blood pressure, and an elevation of these two parameters may give rise to misleading conclusions with regard to myocardial oxygen consumption when contractility and/or ventricular volume are simultaneously lowered. In this regard, it has been demonstrated that the exercise-induced elevation of circulating catecholamines is attenuated after training, an effect that would favor reduction of myocardial oxygen requirements. Other potential effects of reduced catecholamines include diminution of the propensity for coronary spasm and decreased platelet adhesiveness, which might improve coronary flow in areas of critical stenoses.

The limitations of this study mainly center around the nature of the population reviewed. In the process of evaluating 78 patients who had participated in the cardiac rehabilitation program, only 10 met all the criteria required for this analysis. However, this relatively small number of subjects was comparable to the populations in the other existing studies and the findings were statistically significant. Subgroups of patients such as those with angina and those having experienced myocardial infarction were too small to evaluate statistically. Management of the patients in this study in all respects other than exercise training was by their personal physicians, so that uniformity was not possible. However, patients were excluded from analysis if any intervention other than training that could favorably alter myocardial oxygen supply-demand balance was varied during the period of training.

This study demonstrates that in a group of patients with coronary artery disease, a 6 month period of modest exercise training typical of clinical cardiac rehabilitation programs was sufficient to induce a favorable alteration in the heart rate and double product at which electrocardiographic evidence of myocardial ischemia
appeared. The mechanism for this apparent elevation of the myocardial ischemic threshold is not apparent.

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