Randomized Trial of a Hospital-Based Exercise Training Program After Acute Myocardial Infarction: Cardiac Autonomic Effects

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Objectives. **This study sought to determine whether a moderate intensity supervised exercise training program, performed immediately after an uncomplicated acute myocardial infarction, improves recovery in cardiac autonomic function compared with standard advice about activity at home.**

Background. **Exercise training has beneficial effects on cardiac autonomic function and may improve prognosis after acute myocardial infarction.**

Methods. **Thirty-nine male and 10 female patients, mean (±SE) age 57 ± 1 years, with an uncomplicated acute myocardial infarction were randomized to either a 6-week moderate intensity supervised hospital-based exercise training program (exercise group) or to an unsupervised low intensity home walking program (control group). Outcome measures included changes in baroreflex sensitivity (phenylephrine bolus method) and heart rate variability (24-h Holter monitoring) and the endurance time at 85% of peak oxygen consumption.**

Results. **At baseline, there were no significant differences in left ventricular ejection fraction (57 ± 2% vs. 53 ± 2%), frequency of anterior infarction (27% vs. 18%) and peak creatine kinase (1,256 ± 170 vs. 1,599 ± 295 IU) between the exercise and control groups. Baroreflex sensitivity (10.5 ± 1.0 vs. 8.4 ± 1.2 ms/mm Hg) and time domain measures of heart rate variability were also similar. After completion of the program, the exercise group exercised for a median of 15 min (interquartile range 12 to 25) at a workload of 104 ± 7 W compared with 7 min (interquartile range 3.5 to 12) at a workload of 89 ± 8 W in the control group ($p < 0.01$). There were significant ($p < 0.001$) improvements in baroreflex sensitivity and heart rate variability for the 49 patients combined but no differences between the exercise and control groups. Baroreflex sensitivity improved by 3.4 ± 1.0 and 1.7 ± 1.0 ms/mm Hg and the standard deviation of 24-h RR intervals by 36 ± 6 and 40 ± 10 ms, respectively ($p > 0.1$).**

Conclusions. **A hospital-based exercise training program increased endurance capacity but did not improve recovery of cardiovascular autonomic function after uncomplicated acute myocardial infarction.**

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Impaired baroreflex sensitivity and heart rate variability are associated with an adverse prognosis after acute myocardial infarction (1–5). In selected subjects, exercise training has been shown to improve these measures of cardiac autonomic function (6,7) and, in animal models, to protect against ventricular fibrillation during myocardial ischaemia (8–10). Rehabilitation programs that include an exercise component appear to reduce the risk of sudden death after acute myocardial infarction (11). However, it is uncertain whether supervised exercise programs have a substantial incremental benefit on autonomic function compared with standard rehabilitation that includes advice about activity (12,13). The aim of the present study was to determine whether a moderate intensity supervised exercise training program, performed in the immediate post–myocardial infarction period, improves recovery in cardiac autonomic function compared with advice about activity at home.

Methods

Protocol. All patients with an uncomplicated acute myocardial infarction admitted to the John Hunter Hospital from June 1993 to June 1995 were considered for randomization. Exclusion criteria were heart failure, unstable angina, inability to exercise and other severe medical illness (Table 1). In eligible patients all cardiovascular medications apart from aspirin and thrombolytic and anticoagulant agents were withheld until completion of the baseline tests. Baroreflex sensitivity, 24-h heart rate variability and radionuclide ejection fraction were assessed on day 5 to 7 after myocardial infarction. After completion of the initial investigations, patients were given metoprolol, 50 mg twice daily and aspirin, 150 mg/day, unless contraindicated. The use of angiotensin-converting enzyme inhibitors and other cardiovascular medication was at the discretion of the attending physician. Patients were randomized to an in-hospital exercise-based program in addition to

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Abbreviations and Acronyms

ECG = electrogram, electrocardiographic
SDANN = standard deviation of 5-min mean normal RR intervals
SDNN = standard deviation of all normal RR intervals

home walking or to a control group that was advised to follow a home walking program as recommended by the National Heart Foundation of Australia. After 6 weeks of rehabilitation, all cardiovascular medications apart from aspirin were withheld for 5 days and the baseline measurements repeated. Symptom-limited bicycle exercise tests were performed to measure oxygen consumption and endurance capacity. The study was approved by the Hunter Health Authority Ethics Committee for human research.

Measurements. *Baroreflex sensitivity.* Baroflex sensitivity was measured by the phenylephrine bolus method (1,6). After placement of an antecubital intravenous line, the patient rested supine for 30 min, after which rest heart rate over 3 min and blood pressure (mean of three measurements with an arm cuff) were recorded. For baroreflex sensitivity, blood pressure was measured using a finger plethysmograph recorder (Finapress, Ohmeda Monitoring Systems). Electrocardiographic (ECG) limb leads and blood pressures were recorded on a Mingograph 7 recorder (Siemens-Elema) and fed into an Apple Macintosh IIfx computer and an Acqknowledge multichannel data acquisition system (Biopac Systems) for subsequent analysis. Phenylephrine bolus (50 μg) was injected over 5 to 10 s with continuous monitoring of heart rate and blood pressure. The dose was increased by 50-μg increments at 10-min intervals until a >20 mm Hg increase in systolic blood pressure occurred; the final dose was repeated three times. Baroreflex sensitivity was calculated off-line from the digital records by plotting each RR interval against the preceding arterial systolic pressure during the first sustained increase in blood pressure and determining the slope of the regression line. Only regression lines with a correlation coefficient >0.8 or that were significant ($p < 0.05$) were used, and the mean of at least three measurements was calculated.

Table 1. Exclusion Criteria* and Enrollment During the 2-Year Study Period

	No. of Patients
Admitted to hospital with MI	563
Excluded	
Postinfarction angina	129
Heart failure	83
Unable to exercise	24
Not residing in study area	47
Other severe medical illness	31
Death	10
Eligible	121
Refusal	63
Enrolled	58

*Only the first exclusion criterion is given. MI = myocardial infarction.

Heart rate variability. Twenty-four hour ambulatory ECG recordings were performed with Marquette 8500 Holter recorders. Heart rate variability was analyzed on a Holter analysis system (Marquette). All QRS complexes labeled as ectopic activity or unclassified were reviewed and corrected if necessary. No complexes were left unclassified. Only normal to normal RR intervals were used in the analysis of heart rate variability. Measurements in the time domain included the mean RR interval for the 24 h, the standard deviation for all RR intervals (SDNN) and the standard deviation of 5-min mean RR intervals (SDANN). Spectral heart rate variability was computed by fast Fourier transform as total (0.01 to 1.0 Hz), low (0.04 to 0.15 Hz) and high frequency power (0.15 to 0.40 Hz) for each 2-min period, and the average value for 24 h was calculated. Results were expressed as the log (ln) of the various frequency components to normalize the skewness of the data.

Oxygen consumption and endurance capacity. Cycle ergometric exercise tests with monitoring of oxygen consumption were performed on days 5 to 7 after infarction (submaximal test) and after 6 weeks of rehabilitation. Patients were familiarized with the equipment before the tests, which were supervised by a physician (M.B.) with no knowledge of the randomization allocation. Although the first exercise test was submaximal, oxygen consumption was monitored during this test to help familiarize the patient with this form of exercise testing. Exercise commenced at 8 W and increased by 8 W every 2 min. Oxygen consumption was monitored continuously (Sensor Medics), and a 12 lead ECG and blood pressure were recorded at 2-min intervals and at peak exercise (Marquette). At the 8-week test, the patient was encouraged to exercise to exhaustion. The test was halted by the supervising physician if >3-mm ST segment depression occurred. Changes in heart rate and blood pressure were not criteria for stopping the test. Peak oxygen consumption was defined as the maximal value obtained and expressed as oxygen uptake/kg. Endurance capacity was assessed 1 to 2 days after measurement of peak oxygen uptake. The exercise level at 85% and 50% of peak oxygen uptake was determined from the previous test. After a 5-min warm-up at an exercise level that resulted in 50% of peak oxygen uptake, the exercise level was increased over a 5-min period to 85% of peak oxygen uptake. The patient then exercised at this level until exhausted. The duration of exercise at 85% of peak oxygen uptake was recorded as the endurance capacity.

Rehabilitation programs. Patients randomized to exercise training attended an exercise program three to four times a week for 6 weeks supervised by a clinical nurse specialist (K.I.) and physiotherapist. The first attendance was usually on day 7 to 10 after myocardial infarction. Each participant was given an individual exercise prescription consisting of a combination of leg ergometry and circuit training, with the intensity of exercise monitored by pulse rate, symptoms and perceived exertion. The duration of continuous exercise at each session increased from 30 min in the first week to 60 min by the third week and continued at this level until completion of the program. Exercise intensity was adjusted to increase the pulse rate to 70% of maximum by the third week of the program. Patients who attended the hospital-based exercise program were also advised to complete the home walking program, which consisted of a gradual increase in daily walking from 5 min twice a day in week 1, increasing to 30 min twice a day in week 6. Patients randomized to the control group were advised to follow the home walking program and to avoid any other regular moderate intensity exertion during the study period. All patients were asked to complete a questionnaire every 2 weeks about their activity at home. Patients following the home walking program did not receive any further advice about rehabilitation until completion of the program.

Statistics and analysis. We assumed that the change in baroreflex sensitivity would be normally distributed with a standard deviation of 5 ms/mm Hg (1,2,6). A minimal clinically important effect of exercise training on baroreflex sensitivity was judged to be 4 ms/mm Hg (6). To detect this effect with 80% power, using a two-tailed unpaired *t* test at the 5% significance level, required 25 patients in each study arm. A sample of 56 patients was planned to allow for 10% dropout during the study. Changes in heart rate variability and baroreflex sensitivity were assessed by repeated measures analysis of variance. Comparisons between control and exercise groups at baseline were made with an unpaired *t* test and chi-square test as appropriate. Exercise duration times were not normally distributed and were expressed as median and interquartile range, and comparison between groups was made with a Wilcoxon rank sum test. Other results are expressed as mean value ± SE.

Results

Patients. Fifty-eight patients were enrolled in the study. Four patients randomized to the exercise program withdrew because of death (n = 1), unstable angina (n = 2) or cerebrovascular accident (n = 1). Five patients randomized to the control group withdrew because of unstable angina (n = 2), reinfarction (n = 1), coronary artery bypass surgery (n = 1) and withdrawal of consent (n = 1). Details of the remaining 49 patients are shown in Table 2. There were small but not significant differences between the control and exercise groups at baseline. Baseline measures of heart rate variability and baroreflex sensitivity were similar in the two groups, apart from some measures of heart variability in the frequency domain, which were lower in the control group (Table 3). For all 49 patients combined, baroreflex sensitivity was 9.4 ± 0.8 ms/mm Hg, and SDNN was 101.6 ± 5.2.

During rehabilitation, beta-adrenergic blocking agents were prescribed for 19 of the 26 patients in the exercise group and for 20 of the 23 patients in the home walking group. Angiotensin-converting enzyme inhibitors were prescribed in three patients in both groups and calcium antagonists in two patients in both groups.

Patients in the exercise training group attended 22 ± 0.8 exercise training sessions over the 6-week period. In the first 2 weeks they exercised for 42 ± 0.6 min/session, with leg ergometry performed at a level of 58 ± 2 W. In weeks 3 and 4, they exercised for 56 ± 1 min/session, with leg ergometry performed at a level of 74 ± 3 W. In the final 2 weeks they exercised for 60 ± 0.2 min/session, with leg ergometry performed at a level of 87 ± 4 W. In addition, patients in the exercise training group reported walking at home for 37 ± 9 min/day by week 2, 45 ± 9 min/day by week 4 and 48 ± 10 min/day by week 6. Patients in the home walking group reported walking for 28 ± 9 min/day by week 2, 48 ± 21 min/day by week 4 and 58 ± 27 min/day by week 6 (p = NS vs. exercise training group).

Results of exercise testing after completion of the trial are shown in Figure 1. Peak oxygen uptake was higher in the exercise group (23.7 ± 1.4 vs. 21.7 ± 1.4 ml/kg per min), but this difference was not significant (p = 0.2). However, endurance testing demonstrated a substantial training effect. The exercise group exercised for a median of 15 min (interquartile range 12 to 25) at a workload of 104 ± 7 W compared with 7 min (interquartile range 3.5 to 12) at a workload of 89 ± 8 W in the control group ($p < 0.01$). There was no difference in peak heart rate (159 ± 4 vs. 153 ± 5) and peak blood pressure in the two groups (194 ± 5/94 ± 3 vs. 190 ± 5/96 ± 2 mm Hg).

Table 2. Baseline Characteristics

	Exercise Group (n = 26)	Control Group (n = 23)
Age (yr)	56 ± 1	59 ± 1
Female gender	7 (27%)	3 (14%)
LVEF (%)	57 ± 2	53 ± 2
Creatine kinase (U/liter)	1,256 ± 170	1,599 ± 295
Anterior infarct	7 (27%)	4 (18%)
Diabetes	2 (9%)	0
Hypertension	2 (9%)	0
Thrombolytic therapy	24 (92%)	17 (74%)

Data presented are mean value ± SD or number (%) of patients. LVEF = left ventricular ejection fraction.

Table 3. Baseline Baroreflex Sensitivity and Heart Rate Variability

	Exercise Group (n = 26)	Control Group (n = 23)
Baroreflex sensitivity (ms/mm Hg)	10.5 ± 1.0	8.4 ± 1.2
Mean RR (ms)	860 ± 22	794 ± 25
SDNN (ms)	109 ± 7	95 ± 7
SDANN (ms)	92 ± 7	84 ± 7
Total power (ln[ms^2])	6.9 ± 0.2	6.4 ± 0.2*
Low frequency (ln[ms^2])	6.0 ± 0.2	5.3 ± 0.2*
High frequency (ln[ms^2])	4.5 ± 0.2	4.0 ± 0.2
Rest supine HR (beats/min)	65.8 ± 2.05	69.2 ± 2.3
Supine mean BP (mm Hg)	92.9 ± 1.8	93.7 ± 1.8

*$p < 0.05$. Data presented are mean value ± SD. BP = blood pressure; HR = heart rate; SDANN = standard deviation of 5-min means for all normal RR intervals; SDNN = standard deviation for all normal RR intervals.

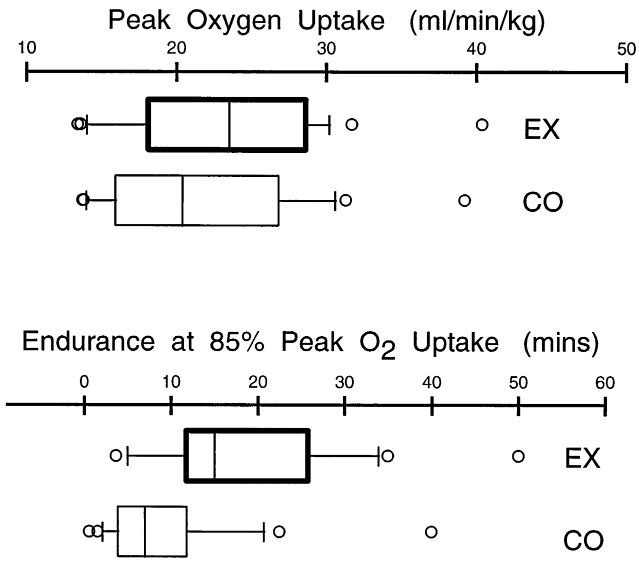

Figure 1. Box plots of peak oxygen (O_2) consumption and endurance capacity at 85% of peak oxygen consumption in the exercise (Ex) and control (CO) groups. There was a significant increase in endurance in the exercise group ($p < 0.01$).

At maximal exercise, r values were 1.22 ± 0.11 in the exercise group and 1.22 ± 0.13 in the control group.

For the 49 patients in total, there were significant improvements in baroreflex sensitivity and in all measures of heart rate variability after rehabilitation (all $p < 0.001$). The improvements in baroreflex sensitivity and heart rate variability were similar in the exercise and control groups, as were the changes in blood pressure and rest heart rate in the two groups (Table 4).

There were weak correlations between peak oxygen uptake and measures of heart rate variability and baroreflex sensitivity after 6 weeks of rehabilitation (e.g., the correlation between peak oxygen uptake and SDNN was $r = 0.37$, $p = 0.01$, and that between peak oxygen uptake and baroreflex sensitivity was $r = 0.26$, $p = 0.07$). There was no correlation between endurance time at 85% of peak oxygen uptake and measures of heart rate variability and baroreflex sensitivity (all $p > 0.1$).

Discussion

The results of the present study suggest that a hospital-based exercise training program, performed over 6 weeks in low risk patients, has minimal additional benefits on cardiac autonomic function compared with a standard home walking program. A comprehensive rehabilitation program that includes intensive risk factor management has been shown (14) to reduce subsequent cardiovascular events. However, the additional value of exercise training is less certain (11,15).

Exercise training effect. The exercise program in the present study achieved a twofold increase in endurance capacity at 85% of peak oxygen uptake. A training effect of this magnitude has been consistently demonstrated with exercise programs of the intensity and duration used in this study (16–20). Exercise training has a much smaller effect on peak oxygen uptake, and the 10% increase in this study was in line with expectations (16,17,20–23). We anticipated that this small increase would not be reliably detected with this study design because peak oxygen uptake could not be measured immediately after myocardial infarction, and there was substantial between-patient variation. For this reason, endurance capacity was chosen as a measure of training effect (20).

Cardiac autonomic function. Measurements of baroreflex sensitivity and heart rate variability could be made at baseline and after rehabilitation, allowing differences to be assessed with the more sensitive repeated measures analysis of variance. Although all measures improved after rehabilitation, there were no significant differences in the degree of improvement in the two groups.

Studies of exercise training in other settings have demonstrated improvements in baroreflex sensitivity (6), heart rate variability (7) and blood pressure (6,16,17,21,24), although these have not been universal findings (12,13,25–27). The present study was conducted in the immediate postinfarction period and consequently differed from most previous investigations with respect to study cohort (predominantly older men) and design (parallel-group rather than crossover study).

The mean age of patients in this study was 58 years (range 41 to 72), and 80% were male. Older male subjects have a

Table 4. Changes in Baroreflex Sensitivity and Heart Rate Variability After Rehabilitation

	Exercise Group (n = 26) (mean ± SD)	Control Group (n = 23) (mean ± SD)	95% CI for Between-Group Difference (ex − control)
Baroreflex sensitivity (ms/mm Hg)	+3.4 ± 1.1	+1.7 ± 1.0	4.5 to −1.3
Mean RR (ms)	−43 ± 17	+1 ± 23	10 to −100
SDNN (ms)	+36 ± 6	+40 ± 9	17 to −25
SDANN (ms)	+40 ± 7	+39 ± 9	23 to −19
Total power (ln[ms^2])	+0.12 ± 0.10	+0.33 ± 0.17	0.17 to −0.59
Low frequency (ln[ms^2])	+0.17 ± 0.13	+0.32 ± 0.18	0.28 to −0.56
High frequency (ln[ms^2])	+0.17 ± 0.10	+0.37 ± 0.19	0.12 to −0.61
Rest HR (beats/min)	−5.3 ± 1.3	−6.0 ± 1.9	5.3 to −3.8
Supine mean BP (mm Hg)	+3.3 ± 1.2	+5.3 ± 1.7	2.2 to −6.0

CI = confidence interval; ex = exercise; other abbreviations as in Table 3.

higher level of rest sympathetic tone (28,29) and diminished baroreflex sensitivity and heart rate variability comparison with younger subjects (1,2,5). Whether age alters the cardiac autonomic adaptations to exercise training is uncertain (29,30), but several other studies of exercise training in older men (12,13,25,26) have demonstrated insignificant changes in baroreflex sensitivity and heart rate variability despite substantial training effects.

Home walking program. Perhaps the most important difference between this and other studies of autonomic function and exercise training relates to the control group, which was not sedentary. Instead, the control patients were advised to follow a home walking program as recommended by the National Heart Foundation of Australia. Home walking programs in motivated subjects can result in a significant training effect (16). The aim of the present study was to determine whether a more intensive supervised exercise program had additional cardiac autonomic benefits over the currently recommended less intensive and unsupervised home walking program. The value of remaining active after acute myocardial infarction is not in dispute (31). However, lack of a completely sedentary control group probably lessened the differences between the exercise and control groups.

Limitations and clinical implications. Finally, it has been well established that there is spontaneous improvement in baroreflex sensitivity and heart rate variability in the recovery phase of myocardial infarction (32,33). The marked improvements in heart rate variability and baroreflex sensitivity observed in this study are likely to be due in part to the natural recovery in autonomic function after myocardial infarction as well as to the rehabilitation programs. This may be a particularly important factor in this relatively low risk group of patients with an average baroreflex sensitivity of 9.4 ± 0.8 ms/mm Hg (1,2). We emphasize that these results should not be generalized to patients with heart failure and complicated myocardial infarction who may benefit more substantially from exercise training (7). However, in low risk patients after myocardial infarction, an additional supervised exercise training does not appear to result in clinically significant changes in cardiac autonomic function compared with a home walking program.

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