Congestive Heart Failure

Effects of exercise training in patients with heart failure: The Exercise Rehabilitation Trial (EXERT)

Robert S. McKelvie, MD, PhD, FRCP(C),[a] Koon K. Teo, MB, PhD, FRCP(C),[c] Robin Roberts, M.TECH,[b] Neil McCartney, PhD,[a] Dennis Humen, MD, FRCP(C),[c] Terence Montague, MD, FRCP(C),[c] Katie Hendrican, MSc,[a] and Salim Yusuf, MBBS, DPhil, FRCP(C)[a] ***Hamilton, Ontario, and Edmonton, Alberta, Canada***

Background The purpose of this study was to examine the effects of exercise training on functional capacity in patients with heart failure.

Methods One hundred eighty-one patients in New York Heart Association class I to III, with ejection fraction <40% and 6-minute walk distance <500 meters, were recruited into a randomized, controlled, single-blind trial comparing 3 months of supervised training, then 9 months of home-based training with usual care.

Results There was a significant increase in 6-minute walk distance at 3 and 12 months but no between-group differences. Incremental peak oxygen uptake increased in the exercise group compared with the control group at 3 months (0.104 ± 0.026 L/min vs 0.025 ± 0.023 L/min; $P = .026$) and 12 months (0.154 ± 0.074 L/min vs 0.024 ± 0.027 L/min; $P = .081$). Compared with the control group, significant increases were observed in the exercise group for arm and leg strength. No significant changes were observed in cardiac function or quality of life. Adherence to exercise was good during supervised training but reduced during home-based training.

Conclusions Exercise training improves peak oxygen uptake and strength during supervised training. Over the final 9 months of the study, there was little further improvement, suggesting that some supervision is required for these patients. There were no adverse effects on cardiac function or clinical events. (Am Heart J 2002;144:23-30.)

See related Editorial on page 1.

Patients with heart failure have reduced exercise capacity, which is more importantly influenced by skeletal muscle impairments than by abnormalities of cardiac function.[1,2] The skeletal muscle abnormalities are similar to those found with physical deconditioning.[1,2] Exercise training leads to a reversal of these skeletal muscle abnormalities,[1,2] and studies suggest that this may be beneficial to patients with heart failure.[1-8] One recent study in a larger group of patients with longer follow-up suggests that the benefits of exercise training could be maintained over the longer term.[9] However, the patients were closely supervised throughout the course of the study, which is not consistent with the typical monitoring of patients in long-term rehabilitation. These studies had several limitations including small size, short duration, and lack of blinded evaluation of outcome measures. Whether the net effects of long-term exercise training, especially in a less closely supervised setting, will result in sustained improvements in patients with heart failure is not known.

The purpose of this randomized, parallel, controlled clinical trial was to examine the effects of exercise training on functional capacity, quality of life, and clinical status at 3 months (short term) and 12 months (long term) in a large group of patients with heart failure.

Methods

Study design

A total of 181 patients were recruited from Hamilton, Ontario, and Edmonton, Alberta, Canada, into a randomized, controlled, single-blind trial (blinded end point evaluation; stratification by center) comparing prescribed exercise training with usual care, with outcome evaluations at 3 and 12 months. Evaluation and training protocols were standardized

From the [a]Division of Cardiology and Preventive Cardiology and Therapeutic Program, Hamilton Health Sciences Corporation, Department of Medicine, and the [b]Department of CEMB, Faculty of Health Sciences, McMaster University Ontario, Hamilton, Ontario, and the [c]Division of Cardiology, University of Alberta Hospitals, University of Alberta, Edmonton, Alberta, Canada.
Submitted June 29, 2001; accepted November 8, 2001.
Supported by the Medical Research Council of Canada.
Reprint requests: R. S. McKelvie, MD, PhD, FRCP(C), Hamilton Health Sciences Corporation, General Site, 237 Barton Street East, Hamilton, ON, L8L 2X2, Canada.
E-mail: mckelrob@hhsc.on.ca

0002-8703/2002/$35.00 + 0 ***4/1/123310***
doi:10.1067/mhj.2002.123310

between centers. Patients were stable on standard medical therapy (angiotensin-converting enzyme inhibitors, diuretics, and digoxin as necessary) at the time of baseline testing. The study was approved by the institutions' research ethics committees, and patients gave written informed consent.

Patient population

Inclusion criteria were documented clinical signs and symptoms of heart failure; left ventricular ejection fraction <40%; New York Heart Association Functional class I to III; and 6-minute walk test distance <500 meters. Exclusion criteria were inability to attend regular exercise training sessions; exercise testing limited by angina or leg claudication; abnormal blood pressure response to exercise testing (systolic blood pressure during exercise >250 mm Hg or diastolic blood pressure response >15 mm Hg, systolic blood pressure response decrease of >20 mm Hg after a normal increase or decrease below the resting level); cerebrovascular or musculoskeletal disease preventing exercise testing or training; respiratory limitation (forced expired volume in 1 second and/or vital capacity <60% of predicted); poorly controlled cardiac arrhythmias; and any noncardiac condition affecting regular exercise training or decreasing survival. During baseline evaluations, a patient's suitability for training was assessed globally (eg, ability to perform exercise; distance from program) to reduce dropout rates after random assignment.

Measurements

The 6-minute walk test was considered the primary outcome measure for this study. Other important outcome measures were peak oxygen uptake, dynamic muscle strength, quality of life, and cardiac function. Outcome measures were performed in a blinded fashion. Individuals responsible for supervising and recording the results of the outcome measurements were unaware of the patient's group assignment.

Six-minute walk test

Patients were instructed to walk as far as possible in 6 minutes on a 33-meter course, with standardized encouragement and breaks as necessary. The outcome measure was the total distance walked in 6 minutes. The test was performed to qualify for study entry, then in duplicate (to reduce variance) on separate days at baseline and at 3 and 12 months.

Incremental exercise testing

Patients performed symptom-limited incremental cycle ergometer exercise testing with electrocardiographic monitoring at baseline and at 3 and 12 months. The work load started at 17 watts (W) and increased by 17 W every 2 minutes. Blood pressure was measured by auscultation every other work load. The 12-lead electrocardiogram was recorded during the final 30 seconds of every other work load and at peak exercise. Heart rate was determined from the electrocardiographic recording. Symptoms were assessed by means of the 10-point Borg scale rating. Peak oxygen uptake was measured with commercially available metabolic carts (Sensor Medics model 2900, Yorba Linda, Calif, or Quinton Q-plex 1, Seattle, Wash) and defined as the highest oxygen consumption during the final 2 minutes of exercise. Individuals were tested on the same cart at each session.

Dynamic muscle strength testing

A weight-and-pulley resistance apparatus was used to assess muscle strength at baseline and at 3 and 12 months. The heaviest weight lifted once through a full range of motion was the patient's 1-repetition maximum for each exercise. Warm-up before strength testing included walking for 5 minutes and 5 repetitions of each strength exercise using very low weight. The initial weights were 1 to 4 kg for arm curl, 35 to 40 kg for leg press, and 7 to 10 kg for knee extension. Single repetitions with progressively heavier weights were performed, with rest 2 to 3 minutes between attempts.

A second strength evaluation was performed within 1 week of the initial test. After the same warm-up procedure, weights were placed at 80%, then 100% of the initial 1-repetition maximum, then small increments in weight were made to attain a true 1-repetition maximum.

Rest radionuclide ventriculography

Ejection fraction and cardiac volumes were measured from a radionuclide ventriculogram acquired in the best septal separation at baseline and at 3 months.

Quality of life questionnaires

Quality of life was measured with the Minnesota Living with Heart Failure questionnaire at baseline and at 3 and 12 months.[10]

Clinical events

It was not anticipated that clinical events would differ between groups, although they were documented. Total mortality rate, hospitalization for heart failure (clinical evidence, changes in heart failure medication, and documented hospitalization >24 hours), and worsening heart failure (clinical evidence, changes in heart failure medication, and no hospitalization) were reported.

Exercise training intervention

Eligible patients were registered in a log and treatment group determined by opening the next sequential study allocation envelope. The predetermined allocation sequence was based on a stream of computer-generated pseudorandom numbers from a uniform distribution stratified by center and with a blocking factor of 4.

Patients performed aerobic and resistance training in the supervised rehabilitation program for the first 3 months and continued with home-based training for the remainder of the study (minimum of 9 months). The aerobic training heart rate was set at 60% to 70% of the measured maximum heart rate response. Patients in the training group performed cycle, treadmill, and arm ergometry exercise for a total time of 30 minutes in each session. Each of these training modalities was performed during every session because it is important to provide an exercise program for the upper and lower body for more complete rehabilitation. During the first 3 months, patients came into the rehabilitation program for supervised training for 2 sessions per week and they performed a third session, which consisted of walking at home each week.

Supervised resistance training, twice a week for 3 months, consisted of arm curl, knee extension, and leg press performed individually with each limb. The initial intensity was 40% of 1-repetition maximum, with 10 repetitions for the arm exercises and 15 repetitions for the leg exercises, with an increase over 5 weeks to an intensity of 60% of 1-repetition maximum and a total of 3 sets of each exercise per session.

After 3 months of supervised training, patients in the exercise group were provided an exercise cycle and set of free weights with instructions to continue training at home 3 times per week for the remainder of the study.

Control patients were not provided with a formal exercise prescription. They were encouraged to continue their usual level of physical activity and were not discouraged from regular physical activity. All patients were reviewed monthly throughout the study.

Statistical analysis

A sample of 180 patients was designed to provide 80% power to detect a difference of 63 meters in 6-minute walk test distance on the basis of a 2-tailed $\alpha = 0.05$. These calculations allowed for an anticipated 14% cumulative mortality rate. Data are presented as mean ± SEM. The primary comparison for all quantitative outcomes was based on the mean change from baseline at 12 months and achieved with a Student *t* test. A secondary comparison was performed at 3 months. In the absence of a difference in intervening death, all comparisons include only surviving patients as opposed to including imputed outcomes for those who died. Kaplan-Meier curves compared the clinical outcomes of total mortality rates, the composite of total mortality rates or hospitalization for heart failure, and the composite of total mortality rates or worsening heart failure between the 2 groups. The survival curves were compared by means of the Mantel-Haenszel test.

Table I. Baseline patient characteristics

Characteristic	Control (n = 91)	Exercise (n = 90)
Age (y)	66.1 ± 0.99	64.8 ± 1.1
Weight (kg)	80.5 ± 1.9	79.6 ± 1.8
Males/females (%)	80/20	82/18
NYHA-FC I/II/III (%)	1/66/33	2/67/31
Drugs (%)		
ACE-I	92	91
Diuretics	86	81
Digoxin	66	62
Nitrates	42	43
β-Blocker	23	20
Calcium-channel blocker	9	13
CHF cause (%)		
Ischemic	73	79
Hypertensive	6	7
Valvular	4	5
Idiopathic	13	6
Other	4	6
CHF duration (%)		
Unknown	1	0
<12 mo	29	28
>12 mo	70	72
Angina pectoris (%)		
None	59	70
CCS I	14	11
CCS II	18	11
CCS III	9	8
Previous MI (%)		
None	29	20
1	41	42
2	18	28
≥3	12	10
Hypertension (%)		
None	60	62
Present	40	38
Diabetes mellitus (%)		
None	73	76
Present	27	24+

Results

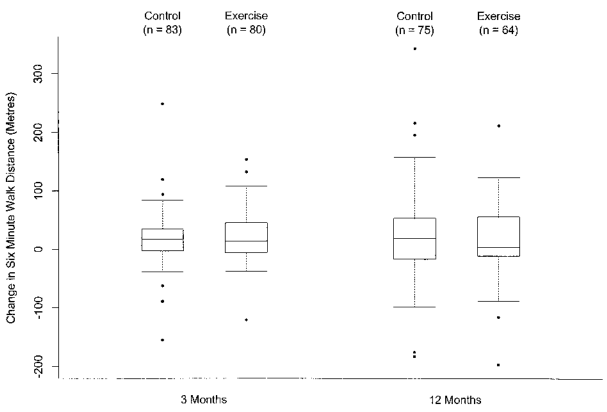
Patients

There were 181 randomly assigned patients (91 in the control group and 90 in the exercise group). There were no differences between the control and exercise training groups with respect to age, resting ejection fraction, New York Heart Association class, cause of heart failure, or duration of heart failure (Table I). For the qualifying 6-minute walk test, 90% of the patients walked between 300 and 499 meters. At least 90% of patients were taking an angiotensin-converting enzyme inhibitor, 80% a diuretic, and 60% digoxin. In the control group, 83 patients completed 3 months of follow-up (reasons for incompletion: death 3; other problems 4; worsening heart failure 1) and 75 patients completed 12 months of follow-up (reasons for incompletion: death 8; withdrawal 2; other problems 3; worsening heart failure 2; refused testing 1). For the exercise group, 80 patients completed 3 months of follow-up (reasons for incompletion: death 1; withdrawal 5; other problems 1; worsening heart failure 2; refused testing 1) and 64 patients completed 12 months of follow-up (reasons for incompletion: death 9; withdrawal 6; other problems 7; worsening heart failure 3; refused testing 1).

Six-minute walk test distance

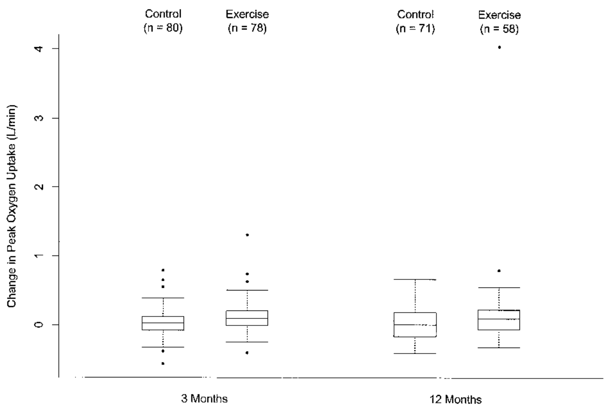
There was no significant baseline difference for 6-minute walk distance between the control (421 ± 8 meters) and exercise (434 ± 7 meters) groups. There was a significant increase in 6-minute walk distance compared with baseline at 3 months ($P < .01$) for both exercise (22 ± 5 meters) and control (15 ± 5 meters) groups (Figure 1). A significant increase in walk distance compared with baseline at 12 months ($P < .05$) was found for both exercise (17 ± 8 meters) and control (20 ± 9 meters) groups. No significant differences were found between groups at either 3 months ($P = .36$) or 12 months ($P = .81$).

Figure 1



Change in 6-minute walk distance in meters at 3 and 12 months.

Figure 2



Change in peak oxygen uptake in liters per minute at 3 and 12 months. Comparison between exercise and control groups at 3 months was significant ($P = .026$). At 12 months there was a trend for peak oxygen uptake to be greater in the exercise group compared with the control group ($P = .081$).

Incremental exercise test performance

There was no significant baseline difference for peak oxygen uptake between the control (1.14 ± 0.04 L/min) and exercise (1.10 ± 0.04 L/min) groups. After 3 months, the peak oxygen uptake of the exercise group increased significantly compared with baseline ($P < .01$) and with the control ($P = .026$) group (Figure 2). At 12 months, a further increase compared with baseline ($P < .05$) was observed in the exercise group, with a trend ($P = .081$) to be greater than control. After exercise training, the training effect was evident in the exercise group compared with control, with a decrease in submaximal exercise heart rate (Table II).

Dynamic muscle strength

Baseline arm strength was similar between the exercise group and the control group; however, after 3 months of resistance training, there was a greater improvement in the exercise group compared with the control group (Table II). This relation was also observed for knee extension and leg press. At 12 months there were again no significant differences between the groups in any of these strength measures.

Assessment of ejection fraction and cardiac volumes

There were no significant baseline differences between groups for ejection fraction, end-diastolic volume, or end-systolic volume (Table II). After 3 months, these similarities were maintained, with no evidence of improvement or deterioration in left ventricular function observed in either group.

Quality of life

After 3 months, there was a slightly greater improvement in the Minnesota Living with Heart Failure questionnaire response in the exercise group compared with the control group, but this was not statistically significant (Table II).

Compliance with exercise training

Forty-three percent of patients attended >80% of the scheduled program-based training sessions, 70% of patients attended >55% of sessions, and 16% of patients attended <50% of sessions. Finally, 14% of patients did not attend any of the scheduled program sessions. During the first month of home-based training, patients were exercising on average 2.3 ± 0.4 sessions per week; however, by 12 months the frequency dropped to 1.7 ± 0.4 sessions per week.

Clinical events

No significant differences were observed between groups for total mortality rates, the composite of total mortality rates or hospitalization for heart failure, and the composite of total mortality rates or worsening heart failure (Figure 3).

Discussion

To date, this is the largest study with the longest follow-up examining the effects of exercise training in patients with heart failure. There was a 9-month home-based training component as part of the 12 months of follow-up with blinded evaluation of patients on a range of clinically useful outcomes. Although there was no improvement in 6-minute walk distance, training did significantly increase both peak oxygen uptake

Table II. Baseline and changes in peak oxygen uptake, muscle strength, cardiac function, and quality of life at 3 months and 12 months

Characteristic	Baseline		Change at 3 m			Change at 12 m		
	Control (n = 91)	Exercise (n = 90)	Control	Exercise	*P*	Control	Exercise	*P*
Submax HR (beats/min) ±SEM	102 ± 2	103 ± 2	−2 ± 2 (n = 77)	−6 ± 2 (n = 77)	.076	−4 ± 2 (n = 65)	−5 ± 2 (n = 52)	.73
Arm curl (kg) ± SEM	8.1 ± 0.4	8.8 ± 0.5	0.50 ± 0.16 (n = 80)	1.20 ± 0.23 (n = 76)	.014	1.07 ± 0.31 (n = 71)	0.61 ± 0.33 (n = 60)	.31
Knee extension (kg) ± SEM	16.6 ± 0.8	17.1 ± 0.8	0.67 ± 0.29 (n = 78)	2.79 ± 0.44 (n = 75)	.0001	0.47 ± 0.54 (n = 69)	1.10 ± 0.61 (n = 59)	.44
Leg press (kg) ± SEM	64.0 ± 1.8	66.8 ± 2.1	1.07 ± 0.65 (n = 79)	2.48 ± 0.79 (n = 76)	.43	1.60 ± 1.12 (n = 60)	1.57 ± 1.14 (n = 60)	.99
Ejection fraction ± SEM	27.7 ± 0.9	28.2 ± 0.8	1.6 ± 0.7 (n = 81)	0.2 ± 0.7 (n = 80)	.17			
EDV (mL) ± SEM	412 ± 23	425 ± 26	5 ± 14 (n = 80)	27 ± 23 (n = 80)	.41			
ESV (mL) ± SEM	313 ± 20	321 ± 20	−10 ± 14 (n = 80)	11 ± 23 (n = 80)	.44			
MLHF ± SEM	28.6 ± 2.1	32.5 ± 2.5	−1.2 ± 1.5 (n = 73)	−3.9 ± 1.9 (n = 70)	.28	−3.3 ± 1.7 (n = 67)	−3.4 ± 2.4 (n = 57)	.98

P value is comparison of exercise versus control. *EDV*, End-diastolic volume; *ESV*, end-systolic volume; *MLHF*, Minnesota Living with Heart Failure questionnaire score.

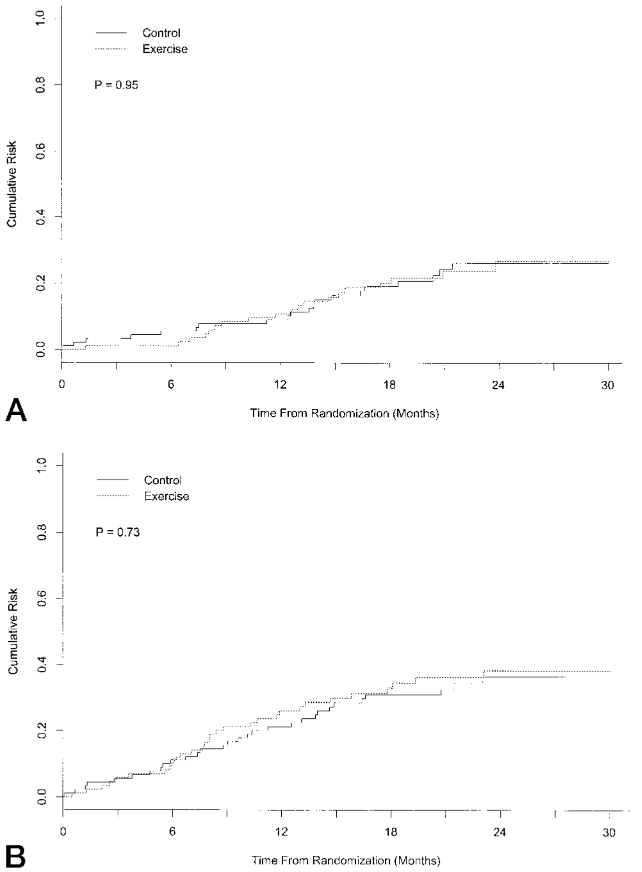
and muscle strength immediately after the structured supervised training program. The training did not have an adverse effect on ejection fraction or cardiac volumes as assessed by radionuclide ventriculography.

No significant improvement was found in 6-minute walk distance after training. Previous studies have suggested that the 6-minute walk test could be used to evaluate functional capacity in patients with heart failure, was related to daily activities, and had prognostic power for clinical events.[11-13] Although 6-minute walk distance has been found to increase in some studies,[14,15] this has not been found in all studies of exercise training.[16] Given the results of more recent studies, a lack of increase in 6-minute walk distance despite an increase in peak exercise oxygen uptake may not be so unexpected. There are data suggesting 6-minute walk test measurements could be quite variable, thus making the test less sensitive to change even though the result may have prognostic value.[17] More recent data have demonstrated that for peak oxygen uptake of 10 to 20 mL/kg per minute (current study averaged 14 mL/kg per minute), there is no significant relation with 6-minute walk distance.[18] Furthermore, a recent study has demonstrated that the 6-minute walk test cannot be used in the individual patient as an alternative to or as a surrogate of peak oxygen uptake.[19] Although detection of an anaerobic threshold during peak oxygen uptake testing guarantees almost maximal exercise performance, a similar guarantee is not available during 6-minute walk testing. Subjective attitudes, self motivation, and mood may more importantly influence the performance of the 6-minute walk test, thus making the test less sensitive to change than is the measurement of peak oxygen uptake. In future studies, submaximal exercise to fatigue on either a treadmill or cycle ergometer should be considered because this may more sensitively detect change in performance.[20]

The increase in peak oxygen uptake after 3 months of training was 10%, with a 14% increase after 12 months of training. This latter increase did not achieve statistical significance because of a substantial number of subjects who failed to have the 12-month assessment. Strength was increased by 14% to 16% at 3 months, with only a minimal increase at 12 months. The lack of improvement in strength at 12 months could be explained by lighter weights (free weights) and the decreased frequency of sessions not providing an appropriate training stimulus during the home-based period of training. There was a decline in the submaximal heart rate response during exercise at 3 months, which was still present at 12 months, but this was not significantly different from the control group.

The findings of the present study are consistent with numerous smaller studies that demonstrated, in the short term, an improvement in exercise performance in patients with heart failure after training.[1,2] A wide range for improvement has been observed and the results of the current study are at the lower end of this range.[1,2] An overview by Piepoli et al[1] of the smaller randomized controlled trials performed

Figure 3



A, Comparison of total mortality rates in exercise and control groups over the course of the study (*P* = .95). **B,** Comparison of composite clinical outcome of total deaths or hospitalization for heart failure over the course of the study (*P* = .73). **C,** Comparison of the composite clinical outcome of total deaths or worsening heart failure over the course of the study (*P* = .40).

by Coats' group of 134 patients demonstrated an overall increase in peak oxygen uptake of 13%, and the current study results are consistent with these findings. Improvements in peak oxygen uptake after training have not been found consistently in all studies.[7,21,22] Wilson et al[21] did not find an overall improvement in peak oxygen uptake in 32 patients with heart failure who trained for 3 months. However, patients with a normal exercise cardiac output response were more likely to improve (9 of 21 patients improved) than those with a reduced response (1 of 11 patients improved). Willenheimer et al[22] found no overall improvement in peak oxygen uptake compared with control (27 patients) in the 22 patients with heart failure participating in 4 months of training. However, 11 patients with ischemic heart disease in the exercise group did have a significant 12% increase in peak oxygen uptake. Belardinelli et al[9] randomly assigned 55 patients with heart failure to training or usual care after classifying them according to echocardiographic criteria.[7] Overall, no increase in peak oxygen uptake was observed, although in the subgroup of patients with an abnormal relaxation pattern a significant 15% increase was observed in peak oxygen uptake. In other studies that used the same training protocol there has been a wide range found for improvement of peak oxygen uptake from 9%[23] to 18%.[3] Thus, the observation in this study of an increase in peak oxygen uptake of 10% to 14% is certainly consistent with the other results in the literature. Therefore, this study probably reflects more accurately the response to training of a moderately large group of unselected patients than do the other studies in which fewer patients were recruited for training.

There were no significant differences observed in cardiac function between the exercise and control groups at 3 months. These findings are consistent with other studies, which found that training does not adversely affect cardiac function.[4,9] Furthermore, the study by Belardinelli et al[9] demonstrated an improvement in the thallium activity score for patients with ischemic heart disease, suggesting myocardial blood flow may be improved after training. Thus, regular training does not appear to have an adverse effect on cardiac function.

There were no differences in clinical events found between the control and exercise groups in this study. However, this is not unexpected because the study was not powered to examine moderate differences in clinical events. In contrast, Belardinelli et al[9] found that training resulted in a reduction in clinical events. The Belardinelli et al[9] results must be interpreted cautiously as the study was not powered to examine these outcomes and the reported differences may be due to chance. Together, the findings of this study and those of Belardinelli et al[9] support the safety of training patients with heart failure.

The current study has demonstrated that it is feasible to train a moderately large group of patients over a period of 1 year in an outpatient setting. However, the improvement in peak exercise capacity was not as great as was found in the randomized study by Belardinelli et al,[9] in which the 99 patients were followed up for 12 months. In the Belardinelli et al[9] study, patients remained in a closely supervised institution-based training program for the complete course of the study. In contrast, this study was designed to assess a home-based training program after a period of supervised training. This may account for the differences in improvement of exercise performance observed between the Belardinelli et al[9] study and this study. Although data were not collected to characterize reasons for missing exercise sessions, they would probably be consistent with those for not completing outcome measures (eg, medical problems, decreased motivation to exercise). These findings suggest that most patients with heart failure will require close follow-up in supervised exercise programs in the long term to assist in encouraging compliance with exercise training.

Conclusions

Combined exercise training improves peak oxygen uptake and strength in patients with heart failure in the short term during supervised training, but this is not accompanied by an increase in 6-minute walk distance or quality of life. Although the improvement in peak oxygen uptake was maintained over a period of 12 months, there was little improvement during the home-based training, suggesting some degree of involvement in a supervised setting is required for these patients. Given the costs and greater effort associated with training these patients, larger studies with built-in mechanisms to encourage better compliance and longer-term follow-up are required to assess whether a clinically important benefit is observed before exercise rehabilitation becomes a routine part of patient treatment.

We thank Ann Page, Dianne Tomson, and Lesly Hill for recruiting and helping to follow up the patients during the study. We also thank Chris Steffann and Tammy Levesque for secretarial assistance.

References

1. European Heart Failure Training Group. Experience from controlled trials of physical training in chronic heart failure: protocol and patient factors in effectiveness in the improvement in exercise tolerance. Eur Heart J 1998;19:466-75.
2. McKelvie RS, Teo KK, McCartney N, et al. Effects of exercise training in patients with congestive heart failure: a critical review. J Am Coll Cardiol 1995;25:789-96.
3. Coats AJ, Adamopolous S, Radaelli A, et al. Controlled trial of physical training in chronic heart failure: exercise performance, hemodynamics, ventilation and autonomic function. Circulation 1992;85:2119-31.
4. Jetté M, Heller R, Landry F, et al. Randomized 4-week exercise program in patients with impaired left ventricular function. Circulation 1991;84:1561-7.
5. Hambrecht R, Niebauer J, Fiehn E, et al. Physical training in patients with stable chronic heart failure: effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. J Am Coll Cardiol 1995;25:1239-49.
6. Kiilavuori K, Toivonen L, Näveri H, et al. Reversal of autonomic derangements by physical training in chronic heart failure assessed by heart rate variability. Eur Heart J 1995;16:490-5.
7. Belardinelli R, Georgiou D, Cianci G, et al. Exercise training improves left ventricular diastolic filling in patients with dilated cardiomyopathy: clinical and prognostic implications. Circulation 1995;91:2775-84.
8. Meyer K, Samek L, Schwaibold M, et al. Physical responses to different modes of interval exercise in patients with chronic heart failure: application to exercise training. Eur Heart J 1996;17:1040-7.
9. Belardinelli R, Georgiou D, Cianci G, et al. Randomized, controlled trial of long-term moderate exercise training in chronic heart failure: effects on functional capacity, quality of life, and clinical outcome. Circulation 1999;99:1173-82.
10. Rector TS, Kubo SH, Cohn JN. Patient's self-assessment of their congestive heart failure: content, reliability and validity of a new measure: the Minnesota Living with Heart Failure questionnaire. Heart Failure 1987;3:198-209.
11. Guyatt GH, Thompson PJ, Berman LB, et al. How should we measure function in patients with chronic heart and lung disease? J Chronic Dis 1985;28:517-24.
12. Bittner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a six-minute walk test in patients with left ventricular dysfunction. JAMA 1993;270:1702-7.
13. Cahalin LP, Mathier MA, Semigran MJ, et al. The six-minute walk

test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest 1996;110:325-32.
14. Kavanagh T, Myers MG, Baigrie RS, et al. Quality of life and cardiorespiratory function in chronic heart failure: effects of 12 months aerobic training. Heart 1996;76:42-9.
15. Meyer K, Schwaibold M, Westbrook S, et al. Effects of exercise training and activity restriction on 6-minute walking test performance in patients with chronic heart failure. Am Heart J 1997; 133:447-53.
16. Kostis JB, Rosen RC, Cosgrove NM, et al. Nonpharmacologic therapy improves functional and emotional status in congestive heart failure. Chest 1994;106:996-1001.
17. Opasich C, Pinna GD, Mazza A, et al. Reproducibility of the six-minute walking test in patients with chronic congestive heart failure: practical implications. Am J Cardiol 1998;81:1497-500.
18. Lucas C, Stevenson LW, Johnson W, et al. The 6-minute walk and peak oxygen consumption in advanced heart failure: aerobic capacity and survival. Am Heart J 1999;138:618-24.
19. Opasich C, Pinna GD, Mazza A, et al. Six-minute walking performance in patients with moderate-to-severe heart failure: is it a useful indicator in clinical practice? Eur Heart J 2001;22: 488-96.
20. Olsen SL, Gilbert EM, Renlund DG, et al. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol 1995;25: 1225-31.
21. Wilson JR, Groves JR, Rayos G. Circulatory status and response to cardiac rehabilitation in patients with heart failure. Circulation 1996;94:1567-72.
22. Willenheimer R, Erhardt R, Cline C, et al. Exercise training in heart failure improves quality of life and exercise capacity. Eur Heart J 1998;19:774-81.
23. Barlow CW, Quayyum MS, Davey PP, et al. Effect of physical training on exercise-induced hyperkalemia in chronic heart failure: relation with ventilation and catecholamines. Circulation 1994;89: 1144-52.