

Randomized, Controlled Trial of Long-Term Moderate Exercise Training in Chronic Heart Failure

Effects on Functional Capacity, Quality of Life, and Clinical Outcome

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Background—It is still a matter of debate whether exercise training (ET) is a beneficial treatment in chronic heart failure (CHF).

Methods and Results—To determine whether long-term moderate ET improves functional capacity and quality of life in patients with CHF and whether these effects translate into a favorable outcome, 110 patients with stable CHF were initially recruited, and 99 (59 ± 14 years of age; 88 men and 11 women) were randomized into 2 groups. One group (group T, $n=50$) underwent ET at 60% of peak $\dot{V}O_2$, initially 3 times a week for 8 weeks, then twice a week for 1 year. Another group (group NT, $n=49$) did not exercise. At baseline and at months 2 and 14, all patients underwent a cardiopulmonary exercise test, while 74 patients (37 in group T and 37 in group NT) with ischemic heart disease underwent myocardial scintigraphy. Quality of life was assessed by questionnaire. Ninety-four patients completed the protocol (48 in group T and 46 in group NT). Changes were observed only in patients in group T. Both peak $\dot{V}O_2$ and thallium activity score improved at 2 months (18% and 24%, respectively; $P < 0.001$ for both) and did not change further after 1 year. Quality of life also improved and paralleled peak $\dot{V}O_2$. Exercise training was associated both with lower mortality ($n=9$ versus $n=20$ for those with training versus those without; relative risk (RR)=0.37; 95% CI, 0.17 to 0.84; $P=0.01$) and hospital readmission for heart failure (5 versus 14; RR=0.29; 95% CI, 0.11 to 0.88; $P=0.02$). Independent predictors of events were ventilatory threshold at baseline (β -coefficient=0.378) and posttraining thallium activity score (β -coefficient -0.165).

Conclusions—Long-term moderate ET determines a sustained improvement in functional capacity and quality of life in patients with CHF. This benefit seems to translate into a favorable outcome. (*Circulation*. 1999;99:1173-1182.)

Key Words: exercise training ■ heart failure ■ quality of life ■ prognosis

A common finding in patients with chronic heart failure is exercise intolerance, which causes a progressive functional deterioration.^{1,2} This vicious circle can be interrupted by discouraging a sedentary lifestyle and promoting physical activity. Controlled clinical studies have recently demonstrated that both in-hospital and home-based exercise training programs of various intensities induce favorable clinical effects by significantly increasing aerobic capacity, delaying the onset of anaerobic metabolism, reducing the sympathetic drive, and increasing the vagal tone.³⁻⁷ Because peak $\dot{V}O_2$ is a good predictor of prognosis in patients with chronic heart failure, the improvement in exercise tolerance after exercise training may be associated with a more favorable outcome. Moreover, it is unclear whether improvements in myocardial perfusion and left ventricular function, recently demonstrated in animals⁸ and humans⁹ with ischemic heart disease after a short-term moderate exercise training program, can affect the clinical outcome.

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The primary objective of the present study was to determine whether long-term moderate exercise training can improve functional capacity in patients with stable chronic heart failure and whether this improvement can translate into a favorable outcome. Other objectives of the study were as follows: (1) to assess the effect of exercise training on quality of life, (2) to identify patients who can benefit the most from exercise training, and (3) to select the independent predictors of outcome.

Methods

Initially, 110 consecutive patients with chronic heart failure in stable condition were recruited. However, after the screening visit at baseline, 11 patients decided not to participate. Thus, 99 patients (mean age, 59 ± 14 years) were studied. All patients were clinically stable in the 3 months before the study. Criteria for eligibility were heart failure, left ventricular ejection fraction $\leq 40\%$, and sinus

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TABLE 1. Baseline Characteristics of the Patients in the 2 Treatment Groups

	Group T	Group NT
n (male/female)	50 (45/5)	49 (43/6)
Mean age \pm SD, y	56 \pm 7	53 \pm 9
Diagnosis, n		
Ischemic cardiomyopathy	43	41
Dilated cardiomyopathy	7	8
Hypertension	5	3
Diabetes	2	3
Peak oxygen uptake, mL \cdot kg ⁻¹ \cdot min ⁻¹	15.7 \pm 2	15.2 \pm 2
NYHA class, n		
I	0	0
II	22	25
III	18	16
IV	10	9
Ejection fraction, * %	28.4 \pm 6	27.9 \pm 5
Medications, † %		
Digitalis	35	30
ACE inhibitors	90	88
Diuretics	92	90
Warfarin	68	65

No significant differences were detected for any of the comparisons shown.

*As assessed by 2-dimensional echocardiography.

†All medications were given at standard doses: digitalis 0.25 mg/d; enalapril 5–20 mg/d; captopril 12.5–25 mg TID; lisinopril 5–20 mg/d; furosemide 25 mg TID; spironolactone 50–100 mg/d.

rhythm. The diagnosis of chronic heart failure was based on clinical symptoms and signs and/or radiological evidence of pulmonary congestion. Clinical characteristics of the patients are summarized in Table 1. The cause of heart failure was ischemic cardiomyopathy (85%) or idiopathic dilated cardiomyopathy (15%). Mitral insufficiency was present in 42 patients and was mild in all. Exclusion criteria were unstable angina, recent acute myocardial infarction, decompensated congestive heart failure, hemodynamically significant valvular heart disease, significant chronic pulmonary illness, uncontrolled hypertension, renal insufficiency (serum creatinine \geq 2.5 mg/dL), and orthopedic or neurological limitations. Medications were not altered throughout the duration of the study and were administered at standard doses.

Protocol

The protocol, approved by the Ethical Committee of the Lancisi Institute, was a prospective, randomized, controlled study. All patients gave written informed consent.

Patients were randomized into 2 homogeneous groups. The exercise group (group T, n=50) underwent exercise training for 14 months. The control group (group NT, n=49) did not exercise. On study entry and at the 2nd and 14th months, all patients performed an exercise test with gas exchange analysis and an echocardiographic study. At the same times, the subgroup of patients with ischemic heart disease (37 in group T and 37 in group NT) underwent thallium myocardial scintigraphy to evaluate the effects of exercise training on myocardial perfusion at different times. All studies were performed by skilled operators and evaluated by 2 experienced observers blinded to each other's interpretation. A third observer was asked to resolve differences when agreement was not achieved. A consensus decision was obtained in all cases.

Exercise Training

Exercise training was performed in 2 phases. Initially, patients exercised 3 times a week for 8 weeks at 60% of peak $\dot{V}O_2$. This

protocol was followed by a 12-month maintenance program of the same intensity but with only 2 sessions a week. Each session lasted \approx 1 hour, beginning with a warm-up phase of stretching exercises (15 to 20 minutes) followed by 40 minutes of cycling on an electronically braked cycle ergometer (Sensorimedics 800S). Blood pressure and heart rate were measured at rest before exercising, at the middle of work on the cycle ergometer, and after 5 minutes of loadless recovery. All sessions were held at the hospital gymnasium under the supervision of a cardiologist.

Echocardiography

M-mode and 2-dimensional echocardiographic studies were performed at baseline and at months 2 and 14 in all patients according to the recommendations of the American Society of Echocardiography.¹⁰ We used an ultrasound system with a 2-dimensional mechanical sector scanner (2.5 MHz, ESAOTE). Left ventricular end-diastolic volume (EDV) and end-systolic volume (ESV) were obtained from the apical 4- and 2-chamber views by a modified Simpson's rule, from which ejection fraction was automatically calculated as the difference between EDV and ESV normalized to EDV. We used a biplane algorithm to calculate left ventricular volumes. Normal values from our laboratory and reproducibility data have been published recently.¹¹

Cardiopulmonary Exercise Test

In the fasting state, an incremental exercise test was performed until volitional fatigue or symptoms or signs of myocardial ischemia appeared.¹² Patients pedaled in the upright position on an electronically braked cycle ergometer (Ergometrics 800 S) at a constant rate of 60 rpm. The work rate was increased 1 W every 5 seconds (ramp). Expired gases were analyzed by use of a metabolic chart (Sensorimedics 2900 Z). Calibration of volumes and gases (O_2 and CO_2) was carefully performed before each test. The ventilatory threshold was measured by the V-slope method.¹³ Peak oxygen uptake was the mean oxygen uptake over the last 30 seconds of exercise.

Thallium Scintigraphy

At the end of the exercise test, 3 mCi of thallium was injected into an antecubital vein. Planar ²⁰¹Tl imaging was begun within 5 minutes in the anterior, 45° left anterior oblique, and 70° left anterior oblique views (Apex Elscint). Redistribution studies were performed 3 hours after stress imaging. Twenty-four hours later, 1 mCi of thallium was reinjected in patients with scintigraphic evidence of a fixed defect noted in the redistribution images. After reinjection, a third set of images was reacquired within 15 minutes.

Data Analysis

At baseline and during follow-up, thallium images were analyzed both qualitatively and quantitatively, as recently described.⁹ Briefly, the serial images were interpreted by visual analysis with the aid of computer quantification.¹⁴ The left ventricle on each view was divided into 5 segments (15 segments in total). Each segment was visually graded on a 5-point scale, where 0 indicated normal uptake, 1 was mild reduction, 2 was evident reduction, 3 was severe reduction, and 4 indicated absent uptake. We defined the thallium activity score index as the sum of the thallium score of each myocardial segment divided by the number of segments analyzed. "White on black" display with a linear gray scale was used. Segments with a score \geq 2 on stress images were considered abnormal. Segments with an initial perfusion abnormality were considered completely reversible when the score was $<$ 2 on delayed scans and partially reversible when the score improved by 1 grade on delayed images. Defects with no change in thallium score between initial and delayed images were considered irreversible. Myocardial segments with irreversible defects were considered to have enhanced thallium activity after reinjection compared with the redistribution study if the regional score decreased by \geq 1. Circumferential count profile analysis was also performed. Thallium images obtained in the follow-up studies were read by the same methods as the baseline study and compared side by side with the corresponding pretraining

TABLE 2. Metabolic and Hemodynamic Results at Baseline and During Follow-Up

	Group T (n=50)			Group NT (n=49)		
	Test 1	Test 2	Test 3*	Test 1	Test 2	Test 3*
Heart rate, rest, beats/min	88±12	80±10	78±10†	93±10	91±11	89±9
Heart rate, peak, beats/min	139±11	142±12	144±13	135±14	133±14	136±12
Systolic blood pressure, rest, mm Hg	112±12	118±16	116±18	108±18	112±16	111±16
Systolic blood pressure, peak, mm Hg	148±19	156±16	158±19	142±15	146±16	145±16
Peak oxygen uptake, mL · kg ⁻¹ · min ⁻¹	15.7±2	18.6±1	19.9±1‡	15.2±2	15.6±2	16±2
Peak carbon dioxide output, mL/min	1427±225	1811±246	1848±255‡	1471±211	1497±227	1545±278
Ventilatory threshold, mL · kg ⁻¹ · min ⁻¹	10.2±2	12.3±2.5	13.4±2‡	9.7±1.4	10.1±1.6	10.2±1.8
Ventilation, L/min	42±8	56±10	59±11§	44±9	46±10	47±10
Respiratory exchange ratio	1.18±0.04	1.20±0.05	1.20±0.05	1.21±0.06	1.20±0.06	1.21±0.05

*Tests 1, 2, and 3 were performed at baseline and at months 2 and 14, respectively. Two patients in the training group and 3 in the control group performed the cardiopulmonary exercise test only at baseline.

† $P < 0.005$ by repeated-measures ANOVA; ‡ $P < 0.001$ by repeated-measures ANOVA; § $P < 0.02$ by repeated-measures ANOVA.

images. Improvement in thallium uptake, compared with the initial study, was defined as an increase in thallium activity by ≥ 1 grade in any of the 3 acquisition imaging series.

Quality of Life

Quality of life was assessed at baseline and after 2, 14, and 26 months in both groups with the Minnesota Living With Heart Failure Questionnaire.¹⁵ This instrument is a patient self-assessment measure and consists of 21 items focused on patient perceptions concerning the effects of congestive heart failure on their physical, psychological, and socioeconomic lives. Recent studies have shown this questionnaire to be responsive to changes in quality of life in patients with chronic heart failure.¹⁶

Follow-Up and Outcome Measures

Follow-up started the day after the end of the maintenance exercise training protocol, that is, after 14 months of exercise training. Patients were monitored for an average of 1214 ± 56 days (range, 1161 to 1268 days). Follow-up ended at the time of study closure or with an adverse event. Measures of outcome were prospectively defined as mortality from all causes and cardiovascular morbidity (development of congestive heart failure requiring hospitalization and adjustment of medical therapy, unstable angina, and myocardial infarction). Detailed information on medical history and clinical profile were collected at the time of enrollment and at every visit during the follow-up period. Patients regularly visited our institution every 3 months during the follow-up period. A record was maintained on each patient's clinical and functional status. Both the exercise and control groups were subjected to the same scrutiny and management regimen apart from the exercise component.

Statistical Analysis

All analyses were performed on an intention-to-treat basis, and probability values were 2-sided. χ^2 statistics and unpaired t tests were used to evaluate differences in baseline characteristics between the 2 groups. Multiple comparisons were assessed by repeated-measures ANOVA. Changes in the exercise group were compared with changes in the control group by use of a nonparametric test (Wilcoxon rank sum test). The effects of training on thallium uptake were analyzed on the basis of patients. We created a scoring system as follows: 0=no change; +1=improvement; -1=deterioration. Univariate analysis of peak oxygen uptake with metabolic, clinical, and scintigraphic variables at baseline and after training by use of change was performed. Variables with significant correlations were then entered into a stepwise linear regression model to determine the best predictor(s) of posttraining change in peak oxygen uptake. Stepwise logistic regression of occurrence of events was also performed. The Kaplan-Meier method was used for survival analy-

sis, and cardiac mortality between trained and untrained patients was compared by log-rank test. The relative risk (RR) and 95% CIs were calculated, when appropriate, to compare outcomes between groups by Cox proportional hazard models. Data were expressed as mean \pm SD. Statistical significance was assumed at $P \leq 0.05$.

Results

One patient in the exercise group did not complete the protocol because of orthopedic limitations after a car accident. Another patient refused to continue after the first week. Three patients in the control group decided to withdraw from the program after a few weeks. A total of 94 patients completed the protocol (48 in group T, 46 in group NT).

Baseline Characteristics

The baseline characteristics of the study population are shown in Table 1. The 2 groups were well balanced with respect to most characteristics, including peak $\dot{V}O_2$, New York Heart Association functional class, and left ventricular ejection fraction. There were no differences in type and doses of medications, blood chemistry, and previous cardiac events.

Adverse Events During Exercise Training

No significant cardiovascular events occurred during the training sessions. Ten patients had sporadic supraventricular and ventricular premature contractions during exercise and recovery. No patient had angina during the training sessions. Compliance with exercise training, defined as percentage of sessions attended, averaged 89% (range, 72% to 100%).

Hemodynamic and Metabolic Parameters

At baseline, no significant differences in hemodynamic and metabolic parameters were observed in the 2 groups (Table 2). Eleven patients (5 in group T, 6 in group NT) with ischemic heart disease had a positive exercise test. After 2 months, all 5 patients with a positive exercise test at baseline had an increase in the ischemic threshold ($18 \pm 5\%$), and 2 had a normal exercise test at the end of the protocol. No changes in the ischemic threshold were observed in control patients. In particular, 3 patients developed low-threshold angina during the final exercise test, and 3 patients with a normal exercise test at baseline had a positive exercise test during follow-up.

TABLE 3. Echocardiographic Results at Baseline and During Follow-Up

	Group T (n=50)			Group NT (n=49)		
	Study 1	Study 2	Study 3	Study 1	Study 2	Study 3
End-diastolic diameter, mm	66.8±5	67.4±5	68.5±5	67.9±4	66.9±5	69.7±6
End-systolic diameter, mm	52.3±5.5	51.9±6	50.2±6	55.2±4.8	56.1±5	57.3±5.5
Fractional shortening, %	21.9±5.2	23.1±6	26.6±5.8	18.7±3.7	16.6±5	17.6±6
EDV, mL	195±19	191±20	188±18	198±18	195±20	197±19
ESV, mL	139±13	133±15	131±14	143±16	144±15	146±16
Ejection fraction, %	28.4±6	30±6.6	30.7±7	27.9±5	26±4.7	26±5.4

No comparisons were statistically significant by repeated-measures ANOVA.

Studies 1, 2, and 3 were performed at baseline and at months 2 and 14, respectively. Two patients in the training group and 3 in the control group performed the echocardiographic study only at baseline.

Oxygen uptake, oxygen pulse, and ventilation were all significantly increased at peak exercise in trained patients compared with controls ($P<0.001$ versus nontrained for all). However, there were no additional changes at the end of the maintenance program. The ventilatory threshold was also increased from baseline in the trained group (30%; $P<0.001$ versus nontrained), whereas the respiratory exchange ratio was similar in both groups in all tests. Resting heart rate was lower in trained patients after 2 months and remained significantly lower at the end of the training protocol ($P<0.01$ versus nontrained).

Echocardiography

No significant changes in left ventricular diameter were observed after 2 or 14 months in either group. Fractional shortening and ejection fraction were also unchanged (Table 3).

Thallium Uptake

At baseline, there was no difference in thallium activity on stress images or after redistribution-reinjection between

the 2 groups (Table 4). After 2 months, the percentage of both myocardial defects with improved thallium activity and reversible defects with higher thallium uptake was significantly higher in trained than in control patients (23% and 21%, respectively; $P<0.001$ trained versus control for both). Furthermore, 75% of trained and only 2% of untrained patients with ischemic heart disease had a greater thallium uptake (95% CI for difference, 0.44 to 0.89; $P<0.001$).

After 14 months, no additional changes in thallium uptake were observed in either group.

Quality of Life

As shown in Figure 1, the questionnaire score improved significantly only in trained patients after 2 months and remained stable after the subsequent 12-month exercise training program and during follow-up. The changes in the score paralleled the changes in peak $\dot{V}O_2$ in trained patients ($r=0.80$; $P<0.001$).

TABLE 4. Thallium Uptake at Baseline and During Follow-Up

	Group T (n=37)			Group NP (n=37)		
	Study 1	Study 2	Study 3	Study 1	Study 2	Study 3
²⁰¹ Tl uptake*						
All	555	555	555	555	555	555
Normal	217	239	240†	210	208	205
Abnormal	338	316	315‡	345	347	350
Completely reversible	78	120	122§	74	70	68
Partially reversible	140	80	78§	138	136	140
Reversible after reinjection	12	10	10	12	12	15
²⁰¹ Tl activity score index¶						
<1.5	0	14 (1.36±0.6)	14 (1.4±0.7)	0	1	2 (1.42±0.2)
1.5–2	24 (1.88±0.99)	16 (1.59±0.11)	17 (1.51±0.13)	18 (1.86±1)	18 (1.84±0.15)	20 (1.89±0.17)
2–2.5	9 (2.25±0.13)	7 (2.31±0.19)	6 (2.27±0.2)	13 (2.34±0.15)	13 (2.42±0.09)	11 (2.4±0.1)
>2.5	4 (2.6±0.2)	0	0	6 (2.65±0.12)	5 (2.62±0.05)	4 (2.71±0.2)

Studies 1, 2, and 3 were performed at baseline and at months 2 and 14, respectively.

*Referred to the number of myocardial segments. Multiple comparisons were evaluated by repeated-measures ANOVA.

† $P=0.02$ vs control.

‡ $P=0.03$ vs control.

§ $P<0.05$ vs control.

¶Referred to number of patients (mean±SD).

|| $P<0.001$ vs control.

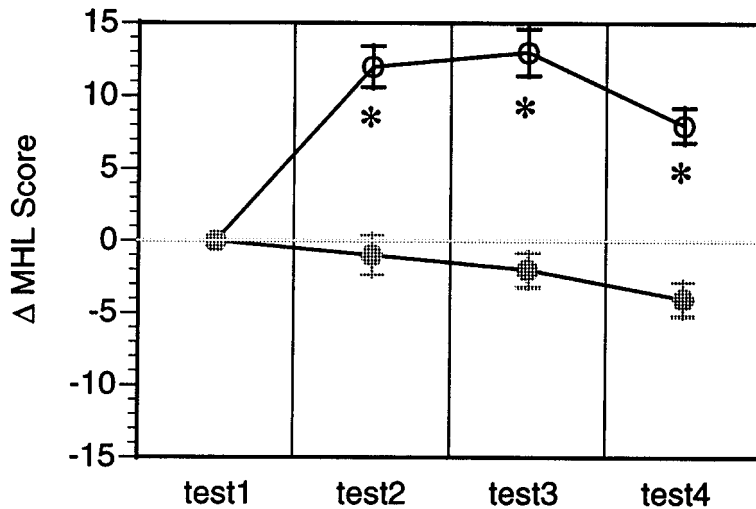


Figure 1. Changes in the Minnesota Living With Heart Failure (MHL) scores for trained (open circles) and untrained patients (closed circles) at baseline (test 1) and after 2, 14, and 26 months (tests 2, 3, and 4). Group T: baseline, 52±22; 2nd month, 40±19; 14th month, 39±20; 26th month, 44±21; group NT: 50±21, 51±22, 52±20, and 54±22, respectively. **P*<0.001 for all comparisons (trained vs untrained).

Outcome

Of the 99 patients included in the analysis, 54 (55%) had cardiac events, 13 during the training period and 41 during the follow-up period. As shown in Table 5, cardiac events were more frequent in the control group (37 versus 17 events; *P*=0.006 versus trained). They comprised 25 nonfatal events (8 in the training group and 17 in the control group) and 29 deaths (9 and 20, respectively). During the initial 2 months of training, 1 event occurred in the exercise group and 3 occurred in the control group. In the subsequent 12 months, 3 events occurred in trained patients and 6 in controls.

The clinical and echocardiographic characteristics of patients with and without cardiac events are summarized in Table 6. Patients who had cardiac events during follow-up had significantly higher values on the ²⁰¹Tl uptake score index as well as end-systolic diameter after training and a lower fractional shortening at baseline than patients who had no events.

Nonfatal Cardiac Events

Of the 25 patients who suffered nonfatal events, 3 had unstable angina, 3 had acute myocardial infarction, and 19 were hospitalized for worsening heart failure. In the control group, 6 patients were hospitalized twice. Patients with ischemic events did not differ from the subgroup of patients without ischemic events with respect to age, clinical condition, and ejection

fraction. Three patients in the training group and 1 in the control group underwent cardiopulmonary bypass surgery. Two patients underwent heart transplantation.

Hospital Readmissions

All 25 patients who suffered nonfatal cardiac events were hospitalized. The rate of hospital readmission for heart failure was significantly higher in control than in trained patients (RR=0.29; 95% CI, 0.11 to 0.84; *P*=0.02) (Figure 2). Multiple readmissions were more frequent in the control group (6 versus 1; *P*=0.001). As shown by the Cox proportional hazards model, the strongest predictors of readmission were peak $\dot{V}O_2$ (*P*=0.001), end-diastolic diameter (*P*=0.01), and systolic wall thickening score index (*P*=0.02).

Cardiac Deaths

Mortality was significantly lower in trained than in untrained patients (RR=0.37; 95% CI, 0.17 to 0.84; *P*=0.01). All deaths (6 during the training phase and 23 during follow-up) were cardiac in nature (congestive heart failure, myocardial infarction, or arrhythmia), and death occurred more frequently in patients with than in those without ischemic heart disease (24 versus 5 deaths, respectively). Six deaths were sudden. Patients who died had higher resting heart rate, end-diastolic diameter, and wall thickening score index and

TABLE 5. Cardiac Events According to Study Group and Cause

	Group T (n=50), n (%)	Group NT (n=49), n (%)	Absolute Difference,* %	RR (95% CI)†	<i>P</i>
All	17 (34)	37 (76)	-42	0.33 (0.18-0.62)	0.006
Unstable angina	2 (4)	1 (2)	2	1.43 (0.13-15.9)	0.77
Acute myocardial infarction	1 (2)	2 (4)	-2.3	0.36 (0.03-4.1)	0.88
Hospital readmission for heart failure	5 (10)	14 (29)‡	-19	0.29 (0.11-0.84)	0.02
Cardiac death	9 (18)	20 (40.8)§	-22.8	0.37 (0.17-0.84)	0.01

*Difference between the percentage of events in trained and control subjects.

†RR and CIs were estimated from the Cox proportional hazards model.

‡Six patients were hospitalized twice.

§Six cardiac deaths were sudden.

TABLE 6. Clinical and Echocardiographic Variables of Patients With and Without Cardiac Events During Follow-Up

Variable	Events	No Events	<i>P</i>
Clinical			
Age, y	57±7	57.7±9	0.86
Sex (male/female)	20/4	26/6	0.88
Myocardial infarction, n	2.46±1.4	1.83±0.86	0.016
Vessels, n	2.33±0.82	2.6±0.99	0.25
Heart rate, rest, beats/min	93.2±5.9	78.7±9.8	0.001
Heart rate, peak, beats/min	131±11	139±17	0.038
Systolic blood pressure, peak, mm Hg	141±12.7	159±19	0.001
Peak oxygen uptake, mL · kg ⁻¹ · min ⁻¹	14.3±1.7	16.6±2.8	0.006
Ventilation, L/min	42.2±6.7	49.7±10.3	0.0016
Ventilatory threshold, mL · kg ⁻¹ · min ⁻¹	9.15±1.4	10.4±1.7	0.0018
Peak work rate, W	92±21	102±19	0.04
Echocardiographic			
End-diastolic diameter, mm	72.4±4	65.1±3	0.001
End-systolic diameter, mm	59±5	51±3.6	0.001
Ejection fraction, rest, %	26±5	29±6	0.03
Systolic wall thickening score index	1.98±0.2	1.76±0.2	0.001
Fractional shortening, %	18.4±6	21.2±5	0.02
Before minus after exercise training			
Δ Peak oxygen uptake, mL · kg ⁻¹ · min ⁻¹	-0.42±1.1	-2.3±2.8	0.002
Δ Heart rate, beats/min	1.12±3.7	2.65±7.4	0.34
Δ Systolic blood pressure, peak, mm Hg	-2.58±6.4	-12.9±16	0.003
Δ Ventilation, L/min	-4.37±10	-7.13±11	0.31
Δ Ventilatory threshold, mL · kg ⁻¹ · min ⁻¹	-0.87±1.15	-2.12±2.2	0.01
Δ Work rate, W	-0.13±8	-17.3±17	0.001
Δ Ejection fraction, %	2.42±2.4	-1.09±3.4	0.001
Δ Thallium uptake score index	0.02±0.14	0.37±0.3	0.001

lower systolic blood pressure and oxygen uptake at peak exercise than patients who survived.

Univariate and Multivariate Analyses

On univariate analysis, the best predictors of improvement in functional capacity were the change in ventilatory threshold and ventilation after training ($r=0.67$ and 0.62 , respectively; $P<0.001$ for both). Stepwise forward logistic regression was performed to assess the independent predictors of posttraining changes in peak $\dot{V}O_2$ using the univariate variables with higher correlation coefficients. The most significant predictors of posttraining change in peak $\dot{V}O_2$ were ²⁰¹Tl uptake score index (β -coefficient -0.15 ; $P=0.006$) and peak $\dot{V}O_2$ at baseline (β -coefficient 1.05 ; $P=0.001$). Patients with a ²⁰¹Tl uptake score index >2.1 and a peak $\dot{V}O_2 <11.3$ mL · kg⁻¹ · min⁻¹ at baseline had the lowest probability of improving their functional capacity (log rank 6.47; $P=0.01$).

The survival model showed an overall effect of exercise training on predicting all cardiac events (log rank 14.29; $P=0.002$) (Figure 3). A lower event-free survival rate was observed in untrained patients with higher end-systolic diameter ($P=0.008$) and ventilation at baseline ($P=0.01$) and lower change in fractional shortening after exercise training

($P=0.02$). Moreover, there was a significant difference between survival curves when separated by exercise training (log rank 6.24; $P=0.01$) (Figure 4). Patients with thallium uptake score <2 at baseline had a significantly lower mortality rate (log rank 15.08; $P<0.001$) and a lower incidence of overall cardiac events (log rank 9.56; $P=0.002$). However, the trend of survival curves was similar when patients were separated by age, cause of heart failure, number of diseased vessels, and number of prior myocardial infarctions. Analysis by Cox proportional hazards model with cardiac death as the dependent variable showed that ventilatory threshold at baseline and thallium uptake score index after training were the only independent predictors (β -coefficients 0.378 and -0.165 , $P=0.0004$ and 0.008 , respectively).

Discussion

The results of this longitudinal study demonstrate that long-term moderate exercise training improves functional capacity in patients with stable chronic heart failure. This beneficial effect translated into a favorable outcome. As a matter of fact, although no significant difference in the frequency of nonfatal cardiac events was observed between the 2 groups over either the training period or the follow-up, a significantly

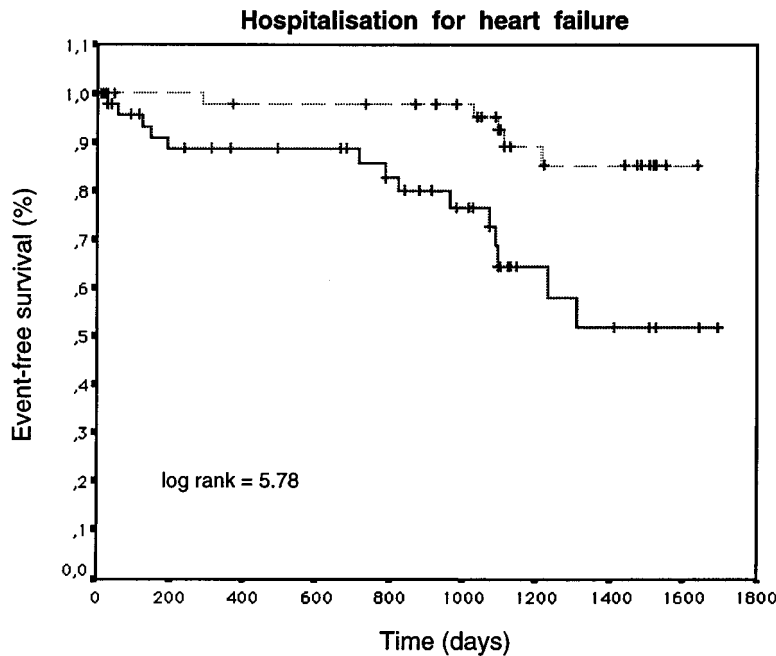


Figure 2. Kaplan-Meier curves of survival without hospital readmission for heart failure in trained patients (broken line) and untrained patients (solid line) during follow-up. + indicates censored cases.

No. OF PATIENTS AT RISK

Untrained	49	44	44	44	42	41	38	36	36	36
Trained	50	50	49	49	49	49	45	45	45	45

lower rate of hospital readmission for heart failure and a lower cardiac mortality rate were observed in patients who improved their functional capacity after exercise training. Quality of life paralleled the improvement in peak oxygen uptake but was not an independent predictor of cardiac events.

Functional Capacity and Quality of Life

The improvement in peak oxygen uptake and ventilatory threshold (18% and 30%, respectively; $P < 0.001$ trained versus untrained for both comparisons) began to be evident after the initial 2 months of the exercise training regimen and did not further increase at the end of the maintenance

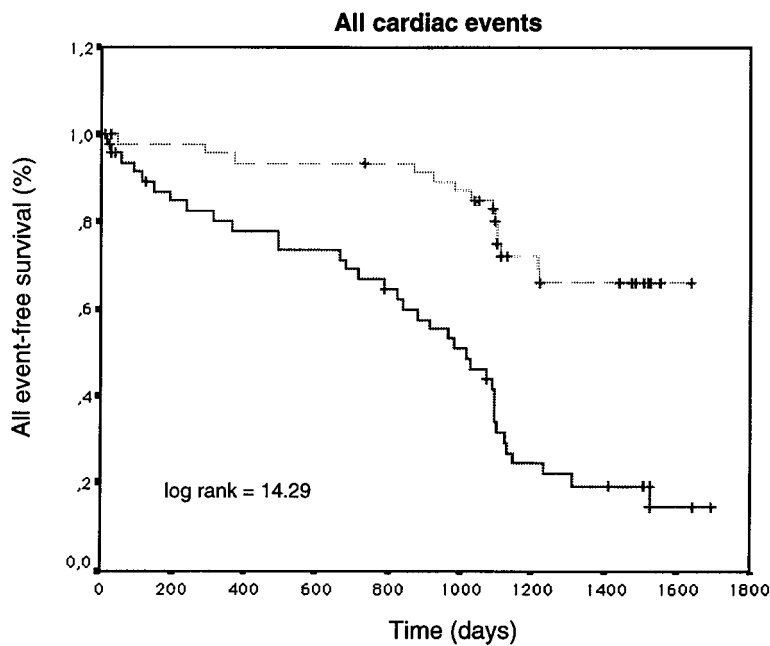


Figure 3. Kaplan-Meier curves of all event-free survival in trained patients (broken line) and untrained controls (solid line) during follow-up. + indicates censored cases.

No. OF PATIENTS AT RISK

Untrained	49	42	40	39	35	29	18	14	12	12
Trained	50	50	48	48	48	39	35	33	33	33

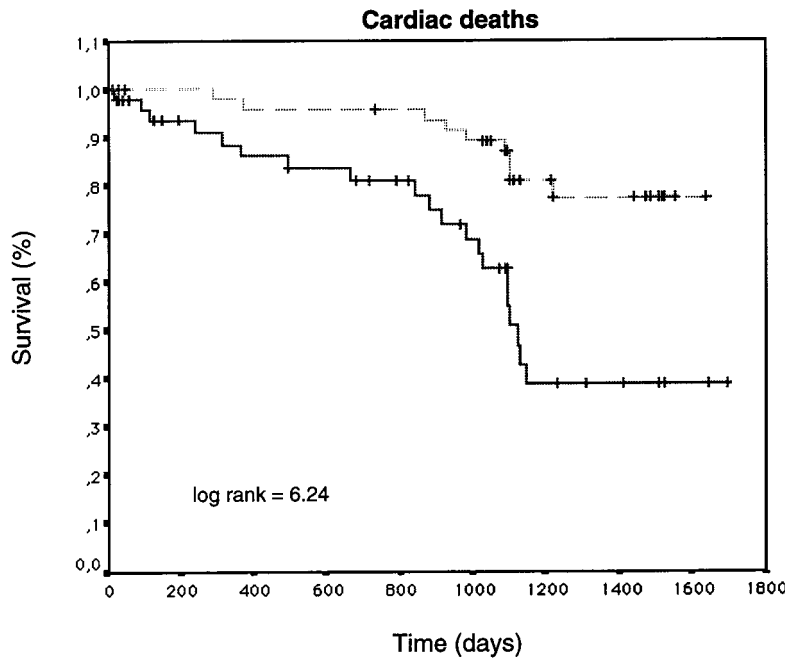


Figure 4. Kaplan-Meier survival curves of cardiac death in trained group (broken line) and untrained control group (solid line) during follow-up. + indicates censored cases.

No. OF PATIENTS AT RISK

Untrained	49	46	43	42	41	37	29	29	29	29
Trained	50	50	48	48	48	45	42	41	41	41

program. These changes appear to be unrelated to loading conditions, because both EDV and systolic blood pressure were unchanged after exercise training.

Previous reports were generally concordant in demonstrating an increase in peak oxygen uptake after short-term exercise training. Coats et al⁴ observed a mean increase of 18% after 8 weeks of home-based exercise training at 60% to 80% of peak heart rate. Sullivan et al³ demonstrated a similar improvement after 4 to 6 months of aerobic training. However, it is unclear whether this beneficial effect can be maintained with a long-term exercise regimen. Recently, the Exert trial demonstrated that peak oxygen uptake significantly increased after the first 3 months of exercise training and then remained stable at 1 year.¹⁷ In the present study, the response of peak oxygen uptake to exercise training was similar. This result is not surprising, because although the intensity of training was the same throughout the study and all sessions were supervised, the 1-year maintenance program had a lower number of sessions per week. Nonetheless, at the end, peak oxygen uptake remained higher in trained patients than in controls. In our opinion, this is a remarkable result that confirms that a low number of sessions per week can be sufficient to maintain a higher functional capacity at levels close to those achieved with short-term physical training of the same intensity. It is conceivable that patients may have better compliance with an exercise regimen with a lower weekly session rate.

The improvement in functional capacity after physical training seems related for the most part to peripheral adaptations.^{3,18-20} However, the posttraining improvement in thallium activity score index observed in the present study in

patients with coronary artery disease suggests that enhanced myocardial perfusion may also play a role. In fact, posttraining changes in peak oxygen uptake and thallium uptake score index were correlated ($r = -0.52$; $P < 0.01$), and the best independent predictors of improvement in functional capacity after exercise training were thallium activity score index and peak oxygen uptake at baseline. Patients with higher myocardial perfusion at baseline seemed to benefit most from exercise training. In fact, both quality of life and functional capacity were similarly higher after training in those patients with greater thallium uptake on initial evaluation. By contrast, patients with a thallium score index > 2.1 and a peak oxygen uptake $< 11.3 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ had no improvement in functional capacity after training.

It is unclear, however, why an improvement in myocardial perfusion after exercise training was not accompanied by changes in ejection fraction at rest. Previous reports also failed to demonstrate any change in left ventricular systolic performance at rest.^{3,9} However, an increase in stroke volume after exercise training has been observed during submaximal exercise²¹ as well as during low-dose dobutamine infusion.⁹ This implies that stroke volume is higher during moderate activities of intensities similar to those of daily life. Thus, by prolonging the duration of training, a greater stroke volume at comparable exercise intensities can be maintained for a longer time.

There are conflicting results on the effects of exercise training on quality of life in patients with chronic heart failure. No changes were observed in the Exert trial.¹⁷ In another study,²² however, the improvement in quality of life followed the course of peak oxygen uptake, which increased

by 15% from baseline and plateaued at 16 to 26 weeks of a 12-month exercise training regimen. This is in agreement with the results of the present study. A long-term, supervised program can improve the quality of clinical care and offer more valid psychological support to patients and their family. The parallel course of quality of life and peak $\dot{V}O_2$ responses to conditioning suggests similar underlying mechanisms.

Outcome

The improvement in exercise capacity after exercise training was associated with a better outcome. Patients who completed the exercise training program had a lower cardiovascular mortality rate than sedentary controls (Figure 4). Among trained patients with posttraining ejection fraction <29% and thallium score index >2.2, the RR was 8.75 times lower than for untrained patients (95% CI, 4.7 to 15; $P < 0.001$), whereas the estimated risk was not significantly different between trained and control subjects when all-cause morbidity was considered (RR = 1.41; 95% CI for difference, -0.23 to 0.09; $P = 0.56$). Moreover, trained patients had a significantly lower rate of hospital readmission for heart failure than did controls.

The reasons why moderate exercise training improves the outcome of patients with chronic heart failure are still a matter of speculation. The relatively higher functional capacity after exercise training may be a stimulus for a more active lifestyle that contributes to the maintenance of a higher peak $\dot{V}O_2$. Another possible explanation may be that moderate exercise training improves myocardial perfusion. The improvement in myocardial perfusion may be due to a mechanism of vessel neof ormation due to intermittent ischemia or vasodilation of preexisting coronary vessels due to reduction of endothelial dysfunction.^{8,23} By prolonging exercise conditioning, all these favorable effects, already seen after short-term physical training, may persist and contribute to maintenance of higher myocardial perfusion. An interaction between ejection fraction and a favorable prognosis has been demonstrated recently after exercise training in patients who suffered a myocardial infarction.²⁴ A favorable outcome in trained patients can in part be the result of a direct inhibition of the deleterious effects of neurohumoral activation. A recent study⁴ demonstrated the efficacy of exercise training in reducing adrenergic tone and increasing vagal tone, as suggested by an increase in heart rate variability indexes and its high-frequency component. This effect has been associated with higher ventricular fibrillation threshold in trained dogs.²⁵

Study Limitations

The population studied was composed predominantly of men with ischemic cardiomyopathy. The percentage of women was 11%. We used planar imaging, which poorly differentiates between underlying or overlying normal or dysfunctional myocardium. However, the planar technique has been validated previously by several groups with homogeneous results.²⁶ Moreover, we performed myocardial thallium imaging at baseline and during follow-up in trained and untrained patients with ischemic heart disease, and the results were interpreted by experienced cardiologists blinded to each other's interpretation and unaware of the clinical picture. We did not measure changes in skeletal

muscle oxidative capacity or changes in autonomic balance after exercise training. As a consequence, the related variables could not be considered in the multivariate analysis. This factor, combined with a small sample size, could have overestimated the importance and the role of the improvement in myocardial perfusion in predicting a lower rate of cardiac events in trained patients with ischemic cardiomyopathy.

In conclusion, the results of this longitudinal study demonstrate that long-term moderate exercise training improves functional capacity and quality of life in patients with stable chronic heart failure. Both benefits were observed immediately after 2 months of physical training and were maintained at 1 year with a supervised program of the same intensity but with a lower number of sessions per week. The sustained improvement in functional capacity seems to translate into a lower rate of hospital readmission for cardiac insufficiency and a lower mortality rate. Quality of life paralleled the improvement in peak oxygen uptake but was not an independent predictor of cardiac events. The beneficial effect of long-term physical conditioning on outcome appears to be related, at least in patients with ischemic heart disease, to a sustained improvement in myocardial perfusion that becomes evident after 24 exercise sessions. The clinical implication is that moderate physical activity should be recommended in conjunction with traditional pharmacological therapy in patients with chronic heart failure.

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