Antiremodeling Effect of Long-Term Exercise Training in Patients With Stable Chronic Heart Failure

Results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial

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Background—The effects of exercise training (ET) on left ventricular (LV) remodeling in chronic heart failure are not definitively established, and the safety of ET in these patients is still debated.

Methods and Results—This multicenter study investigated the long-term effect of moderate ET on LV remodeling, work capacity, and quality of life (QoL) in 90 patients with stable chronic heart failure caused by LV systolic dysfunction, randomized to a 6-month ET program (T, n=45) or a control group (C, n=45). All patients underwent resting echocardiography, a cardiopulmonary exercise test, 6-minute walking test, and QoL assessment at entry and after 6 months. At entry, end-diastolic (EDV) and end-systolic (ESV) volume, ejection fraction, work capacity, peak $\dot{V}O_2$, and walking distance were similar in the 2 groups. After 6 months, LV volumes diminished in T (EDV, from 142±26 to 135±26 mL/m^2, $P<0.006$; ESV, from 107±24 to 97±24 mL/m^2, $P<0.05$) but increased in C (EDV, from 147±41 to 156±42 mL/m^2, $P<0.01$; ESV, from 110±34 to 118±34 mL/m^2, $P<0.01$). Ejection fraction improved in T ($P<0.001$) but was unchanged in C (P=NS). Significant improvement in work capacity ($P<0.001$), peak $\dot{V}O_2$ ($P<0.006$), walking distance ($P<0.001$), and QoL ($P<0.01$) was observed in T but not in C (P=NS). T showed a trend toward fewer ($P=0.05$) hospital readmissions for worsening dyspnea in the absence of other adverse cardiac events.

Conclusions—In stable chronic heart failure, long-term moderate ET has no detrimental effect on LV volumes and function; rather, it attenuates abnormal remodeling. Furthermore, ET is safe and effective in improving exercise tolerance and QoL. **(*Circulation*. 2003;108:554-559.)**

Key Words: exercise ■ heart failure ■ remodeling

Left ventricular (LV) remodeling has a key role in the progression of heart failure. The process of LV remodeling is not related to a single factor but rather to a complex interrelated multifactorial cascade, involving hemodynamic, nonhemodynamic, energetic, and neurohormonal derangements.[1] These diverse, intertwining components provide multiple opportunities for therapeutic interventions. Over the past 2 decades, neurohormonal antagonists, most notably ACE inhibitors and β-blockers, have been combined to yield impressive benefits in patients with chronic heart failure (CHF). In this setting, exercise training (ET) may potentially have an additional role, because an unacceptable burden of disability and unrelieved symptoms still remain even in optimally medically treated patients, with negative repercussions on both quality of life and prognosis.[2,3] Carefully designed ET programs have been found to reduce symptoms, increase exercise tolerance, and improve quality of life without detrimental effect,[4–8] and it is now believed that exercise restriction may lead to deconditioning and increased morbidity.[4] Although training benefits have been attributed predominantly to adaptations in the peripheral circulation and skeletal muscle rather than to adaptations in cardiac performance,[8,9] a possible attenuation of LV remodeling has also been documented in selected patients with LV dysfunction[10] and heart failure.[11,12] However, owing to the limited number of patients enrolled in previous randomized studies—studies for the most part conducted at a single experienced center—the impact of ET on LV remodeling and contractile function in patients with CHF has not been specifically addressed.

Thus, the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) study was designed as a multicenter, randomized trial to determine whether long-term ET may influence LV volume and function in a large cohort of patients with stable CHF. A secondary aim was to assess the safety of an ET program in such patients.

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Methods

Study Protocol

The ELVD-CHF was a multicenter, randomized, controlled study in patients with compensated CHF and LV systolic dysfunction, as defined by an echocardiographic ejection fraction of ≤35%, who were enrolled at 1 of 15 cardiac rehabilitation centers throughout Italy. All patients underwent functional evaluation both at baseline and at 6-month follow-up. The functional evaluation included (1) accurate physical examination, (2) resting echocardiographic study, (3) symptom-limited cardiopulmonary exercise testing on bicycle ergometry, (4) 6-minute walking test, and (5) quality-of-life assessment. All data were collected and analyzed at the Coordinating Center. After initial evaluation, patients were randomly assigned to either a 6-month ET program or a control group. Follow-up was performed at each participating center that was responsible for the clinical evaluation and management of the ET program. New episodes of clinical decompensation, reinfarction, angina, or the need for coronary revascularization procedures were considered clinical end points. The appropriate use of β-blockers and ACE inhibitors was strongly recommended in both study groups.

All patients provided signed, informed consent before randomization. The study was approved by the local scientific and ethics committees.

Study Patients

Statistical power calculations, for the primary end point of LV end-diastolic volume based on our previous data on the reproducibility of ventricular size by 2D echocardiography in postinfarction patients with LV dysfunction, revealed a power of 0.8 to detect a 5% change at 5% significance level, with 80 patients completing the trial.

Consecutive patients with compensated CHF were admitted into this prospective study if the following criteria were met: (1) heart failure secondary to idiopathic dilated cardiomyopathy, ischemic heart disease, or valvular disease; (2) echocardiographic ejection fraction ≤35%; (3) clinical stability for at least 3 months under optimized therapy; (4) New York Heart Association functional class II to III; (5) peak oxygen uptake ($\dot{V}O_2$) <20 mL · kg^{-1} · min at ergospirometry; and (6) echocardiographic images of adequate quality for quantitative analysis. Exclusion criteria were any systemic disease limiting exercise, hypertrophic cardiomyopathy, valvular disease requiring surgery, angina pectoris, sustained ventricular arrhythmias, severe hypertension, excess variability (>10%) at baseline cardiopulmonary exercise test, and inability to participate in a prospective study for any logistic reason.

Cardiopulmonary Exercise Testing

Ten to 15 days before study enrollment, patients underwent a familiarization incremental symptom-limited cardiopulmonary exercise test on an electronically braked computerized bicycle ergometer. After 2 minutes of rest and a 1-minute warm-up period of unloaded pedaling, the work rate was increased 10 W/min in a ramped manner. A 12-lead ECG was continuously monitored and recorded on paper from all leads each minute, and cuff blood pressure was recorded manually every 3 minutes. $\dot{V}O_2$ was determined as the average value observed over the last 20 seconds of exercise and was expressed in mL · kg^{-1} · min. The ventilatory anaerobic threshold was calculated by the V-slope method.[13] Exercise was stopped when patients were physically exhausted or complained of severe dyspnea or dizziness. To assess the reproducibility of gas exchange parameters, the cardiopulmonary test was repeated in all patients 3 to 5 days before starting the protocol and was considered as baseline. The examination was repeated with the same modalities at the end of the study.

Six-Minute Walking Test

A standardized procedure was followed. Walks took place at approximately the same time of the day, at least 2 hours after a meal. Before the baseline test, patients were familiarized with the test and the environment. After a 15-minute rest, they were asked to walk from one end to the other of the walking track, covering as much ground as possible in 6 minutes. Patients were allowed to rest whenever required and to stop if angina, dyspnea, or musculoskeletal pain occurred or if they desaturated to levels <85%. Two walks were performed, with at least 30 minutes of rest between each walk. The averaged results of the 2 consecutive tests both at baseline and at 6-month follow-up were considered for analysis.[14]

Echocardiography

2D resting echocardiographic recordings were obtained at both the initial and final evaluations with commercially available instruments. In each patient, multiple views were recorded on VHS 0.5-in videotapes. All echocardiograms were submitted to the core laboratory at the Coordinating Center for a centralized quantitative analysis. Images were then digitized (Tomtec-Freeland Medical offline computer analysis system) to obtain endocardial contours and LV cavity areas at end diastole and end systole from the apical 4- and 2-chamber views. The modified Simpson's rule was used to obtain biplane LV volumes, and ejection fraction was derived from the standard equation. Mitral regurgitation was detected by color flow Doppler and graded as mild, moderate, or severe according to previously reported criteria that took into account the size of the jet at the regurgitant orifice. All measurements were obtained in a blinded manner by a single experienced operator (P.L.T.) from 3 cardiac cycles. Intraobserver variability in the estimation of end-diastolic and end-systolic volumes was 2.4±2.1% and 2.5±2.4%, respectively.

Training Intervention

A supervised ET program was designed in collaboration with the rehabilitation centers taking part in the study. The exercise protocol consisted of supervised continuous sessions of 30-minute bicycle ergometry ≥3 times a week (3 to 5 times) at 60% of the peak $\dot{V}O_2$ achieved at the initial symptom-limited exercise testing. During each session, intensity of exercise, heart rate (from ECG monitoring), and blood pressure were recorded. During the first 2 months, this exercise protocol was performed with a gradual increase of both workload and duration of exercise sessions, always below the limit at which symptoms could appear. Thereafter, the workload during bicycle ET sessions was adjusted on the basis of a new symptom-limited cardiopulmonary exercise test. In addition to supervised sessions, patients were asked to take a brisk daily walk for >30 minutes and intermittent unsupervised sessions of calisthenics (30 minutes) as part of the home-based exercise program. They were instructed to fill in a diary, reporting the date, time, duration, and pulse heart rate at the end of each nonsupervised exercise session. The compliance for home training averaged 85%.

Patients in the control group received educational support but no formal exercise protocol; they were invited to continue their individually tailored cardiovascular medications and their usual lifestyle but to avoid any physical activity that caused breathlessness or fatigue.

Clinical and Quality-of-Life Assessment

Full clinical assessment was performed at the time of enrollment and after 3 and 6 months and included heart rate, blood pressure, symptoms evaluation (NYHA classification), and physical examination. From the physical examination, a clinical score (graded on a 3-point scale) based on third heart sound, venous jugular pulse, peripheral edema, pulmonary rales, and hepatomegaly was derived.

Quality of life was assessed with modified Likert symptom questionnaires (graded on a 6-point scale) on breathlessness, tiredness, chest pain, daily activity, and emotional status.

Statistical Analysis

Baseline characteristics of the 2 groups were compared using the unpaired Student's *t* test for continuous variables and the χ^2 test for discrete variables. All data were analyzed comparing the initial (at entry) with the final (after 6 months) study. Differences between the 2 groups and changes over time within each group (time effect), as

TABLE 1. Patient Baseline Characteristics

	Exercise Training Group (n=45)	Control Group (n=45)
Age, y	60±7	61±7
Diagnosis		
Ischemic heart disease	30 (67%)	30 (67%)
Dilated cardiomyopathy	12 (27%)	13 (29%)
Valvular disease	3 (6%)	2 (4%)
Hypertension	30 (66%)	27 (60%)
NYHA functional class		
II	28 (62%)	33 (73%)
III	17 (38%)	12 (27%)
$\dot{V}o_2$ peak, mL · kg^{-1} · min^{-1}	13.8±2.3	13.7±2.2
LVEF, %	25±4	25±5
Moderate to severe mitral regurgitation	5 (11%)	4 (9%)

NYHA indicates New York Heart Association; $\dot{V}o_2$ peak, peak oxygen uptake; LVEF, left ventricular ejection fraction. Values are mean±SD or No. (%) of patients. Differences between groups are not statistically significant.

well as any interaction (different trends over time between groups), were assessed by multivariate repeated-measures ANOVA. Differences were considered significant at a value of $P<0.05$. Results are expressed as mean±SD.

Results

One hundred patients were evaluated over a 1-year period for possible enrollment. Ten patients were excluded because of exertional angina (n=2), baseline sustained ventricular arrhythmias (n=1), hypertrophic cardiomyopathy (n=2), systemic disease limiting exercise (n=2), and excess variability at cardiopulmonary exercise test (n=3). The remaining 90 patients were enrolled and, after completion of initial evaluation, randomly assigned to either a 6-month training program (n=45) or control (n=45).

The initial data for the 90 patients enrolled in the study are reported in Table 1. No significant differences were observed between the 2 groups with respect to demographic and clinical data, including age, weight, cause of heart failure, or New York Heart Association functional class. Furthermore, there was no difference between the 2 groups in the medications received during the 6-month period of the study (Table 2). Drug treatment was not changed during the study in any patient (excluding temporary changes during hospitalization, related primarily to the doses of diuretics and vasodilators).

Clinical Events

Clinical events occurred in 15% of patients in the control group and in 9% in the training group ($P=0.048$). In the control group, 1 patient died of sudden cardiac death 1 month after enrollment. Six patients had a temporary worsening of symptoms that did not require hospitalization, and another patient was admitted to hospital because of temporarily worsening dyspnea and peripheral congestion.

In the exercise group, 2 patients had temporary clinical deterioration not requiring hospitalization, and another 2 patients (baseline LV ejection fraction 24% and 28%, respectively) were hospitalized because of worsening symptoms at 3 and 4 months after the beginning of the study, respectively. These patients were comparable to the other randomized patients with respect to duration of disease and baseline parameters. They continued the study after hospital discharge. Complete 6-month follow-up measurements were obtained in all surviving patients in both groups (Figure).

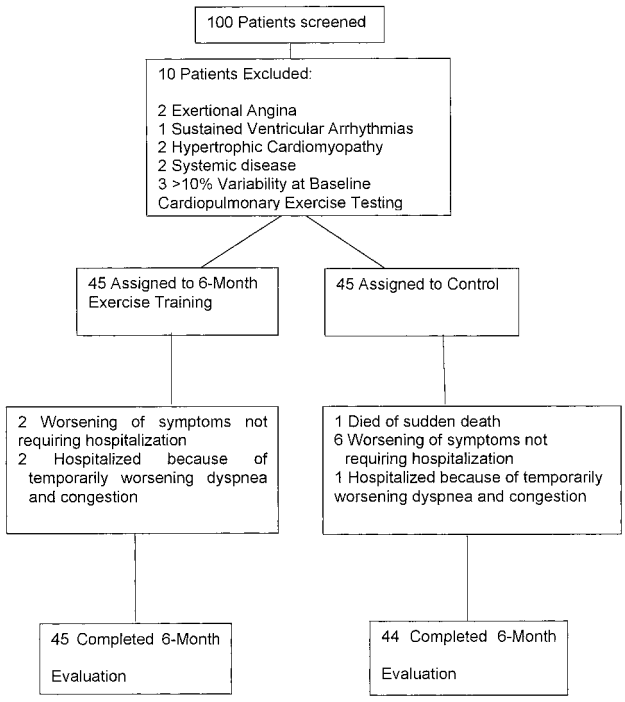
TABLE 2. Medications During the 6-Month Period of the Study

	Exercise Training Group (n=45)	Control Group (n=44)
ACE inhibitors	41(91%)	42(93%)
Digitalis	30(67%)	31(69%)
Diuretics	41(91%)	41(93%)
β-Blockers	10(22%)	9(20%)
Nitrates	23(51%)	22(49%)
Antiarrhythmic agents	15(33%)	14(31%)
Statins	15(33%)	16(35%)
Warfarin	16(35%)	17(38%)

Data are No. (%) of patients. Differences between groups are not statistically significant.

Echocardiographic Data

Baseline LV volumes and ejection fractions were similar in the 2 groups (Table 3). After 6 months, end-diastolic and end-systolic volumes had increased in the control group by 6% and 7%, respectively, whereas they had decreased by 5% and 9% in the training group ($P<0.001$ and $P<0.01$, interaction for end-diastolic and end-systolic volumes, respectively). Ejection fraction had not changed in the control group but had improved by 16% in the training group ($P<0.01$, interaction).



Patients included in and excluded from the study.

TABLE 3. LV Function and Remodeling

	Exercise Training Group (n=45)		Control Group (n=44)	
	Baseline	6 Months	Baseline	6 Months
EDV, mL/m^2	142±26	135±26*	147±41	156±42*†
ESV, mL/m^2	107±24	97±24*	110±34	118±34*‡
EF, %	25±4	29±4*	25±4	25±5‡

EDV indicates end-diastolic volume; ESV, end-systolic volume; and EF, ejection fraction. Data are mean±SD.

*$P<0.01$, time effect within group; †$P<0.001$, interaction; ‡$P<0.01$, interaction.

Exercise Performance

Heart rate at rest was similar for the 2 groups at both baseline and final evaluation. Systolic blood pressure along with rate-pressure product at rest decreased slightly after 6 months only in the training group ($P<0.05$). In both groups, no 6-month changes were observed at peak exercise with respect to heart rate, systolic blood pressure, and rate-pressure product (Table 4).

Baseline exercise performance was similar in the 2 groups in terms of exercise time, work capacity, and oxygen uptake. In control patients, exercise time, workload, and oxygen uptake at the ventilatory threshold and at peak exercise were unchanged after 6 months. In contrast, in the trained patients, exercise time had increased by 2.1 minute (29%, $P<0.001$), work capacity by 18 W (24%, $P<0.001$), and oxygen uptake at the ventilatory threshold and at peak exercise by 2.4 mL · kg^{-1} · min (17%, $P<0.006$) and by 2.1 mL · kg^{-1} · min (19%, $P<0.001$), respectively. In a comparison of the initial with the final study at the same submaximal workload, heart rate, systolic blood pressure, and rate-pressure product did not change in the control group, whereas they decreased significantly ($P<0.01$) in the training group.

Walking distance during the 6-minute walking test increased by 20% ($P<0.001$) in the ET group but was unchanged in the control group (Table 3).

Clinical Score and Quality of Life

All baseline factors examined were similar in the 2 groups (Table 5). After 6 months, clinical score improved significantly only in trained patients ($P<0.01$). Similarly, quality of life, assessed by modified Likert questionnaires, improved significantly after ET ($P<0.05$), whereas it remained unchanged in control patients.

Discussion

The results of this multicenter, randomized, controlled study demonstrate that long-term moderate ET in stable CHF patients with severe LV systolic dysfunction has an antiremodeling effect, as documented by a small but significant reduction in LV volumes and an improvement in ejection fraction. Furthermore, ET is feasible, safe, and effective in improving both maximal and submaximal exercise tolerance and quality of life.

In postinfarction patients with LV dysfunction, ET does not cause any harmful effect on LV volumes[10,15]; rather, it attenuates the remodeling process.[10] Recent studies, although not aimed at monitoring the LV remodeling process, have

TABLE 4. Maximal and Submaximal Exercise Test

	Exercise Training Group (n=45)		Control Group (n=44)	
	Baseline	6 Months	Baseline	6 Months
Rest				
HR, bpm	69±9	67±10	70±9	69±10
SBP, mm Hg	120±10	115±11*	117±12	118±12‡
RPP, mm Hg×bpm×10^3	8.4±1.3	8.0±1.0*	8.2±1.3	8.1±1.2
Peak exercise				
HR, bpm	138±14	140±15	135±18	139±16
SBP, mm Hg	145±18	149±16	144±15	146±16
RPP, mm Hg×bpm×10^3	20.1±3.2	20.8±3.4	19.6±3.8	20.3±3.9
Work capacity, W	75±20	93±23*	77±17	78±18†
Exercise time, min	7.3±1.9	9.4±2.2*	7.3±1.8	7.4±1.9†
Peak oxygen uptake, mL · kg^{-1} · min^{-1}	13.8±3.3	16.2±3.6*	13.8±2.3	13.7±2.2†
Respiratory exchange ratio	1.13±0.08	1.12±0.09	1.16±0.08	1.17±0.07‡
Same submaximal workload				
HR, bpm	130±15	121±13*	132±15	130±14‡
SBP, mm Hg	142±18	133±16*	139±16	137±17‡
RPP, mm Hg×bpm×10^3	18.5±2.8	16.3±3.0*	18.4±2.6	17.9±2.8‡
6-minute walking distance, m	385±83	461±102*	369±99	368±107†

HR indicates heart rate; SBP, systolic blood pressure; and RPP, rate-pressure product. Data are mean±SD.

*$P<0.01$, time effect within group; †$P<0.001$, interaction; ‡$P<0.01$, interaction.

TABLE 5. Clinical Score and Quality-of-Life Assessment

	Exercise Training Group (n=45)		Control Group (n=44)	
	Baseline	6 Months	Baseline	6 Months
Clinical score	7.0±2.7	5.3±2.1*	7.2±2.1	7.2±2.1†
Symptoms perceived during daily physical activity	13.4±1.8	10.9±1.3*	13.8±1.4	13.4±1.8‡

Data are mean±SD. For clinical score and symptoms perceived during daily physical activity, a low score is better.

*$P<0.01$, time effect within group; †$P<0.01$, interaction; ‡$P<0.05$, interaction.

suggested that training may benefit cardiac function or attenuate abnormal remodeling even in patients with CHF.[11,12] To the best of our knowledge, the present study is the first one designed specifically to investigate the effects of long-term ET on LV remodeling in a large cohort of patients with CHF of different pathogeneses. We confirm that ET does not have a detrimental effect on remodeling; on the contrary, we observed an attenuating effect on LV dilation and a favorable effect on LV function, as expressed by a small but significant increase in ejection fraction in the training group (not observed in the control). Because medications were equally distributed in the 2 groups, an additional favorable antiremodeling effect of ET over medical therapy should be considered.

ET as an Antiremodeling Intervention

Several mechanisms may be responsible for the antiremodeling effect of ET. The features of the training response in our study are consistent with a normal response to regular exercise, including reduction in resting heart rate (although this was not statistically significant in our study) and blood pressure and reduction in exercise heart rate and rate-pressure product. The significant decrease in resting blood pressure and submaximal rate-pressure product in the exercise group may favorably affect LV wall tension and limit its deleterious effects on LV structure and function over time.

It has been demonstrated that ET enhances oxidative capacity of the skeletal muscle vasculature and corrects endothelial dysfunction of the skeletal musculature in both ischemic and idiopathic dilated cardiomyopathy.[8,9,12] This may contribute further to a reduction of peripheral resistance and to an improvement in stroke volume[12] and could also explain the improvement of myocardial perfusion observed even in the absence of changes in coronary artery diameter.[11] The improvement in myocardial flow supply in both infarcted and noninfarcted zones, even late after an acute ischemic event, may ultimately lead to some degree of recovery of both global and regional LV function.[16] Finally, recent investigations have shown that the infiltration/activation of monocytes contributes to the development of LV remodeling and heart failure.[17,18] Of note, ET intervenes in the various stages of the inflammatory process in patients with CHF and exerts a favorable control of remodeling by reducing the major circulating proinflammatory cytokines and their soluble receptors.[19]

Comparison With Previous Studies

Previous studies were concordant in demonstrating an increase in exercise capacity, exercise time, maximum ventilation, and quality of life after 2 to 6 months of aerobic training in stable CHF,[4–8] in the absence of major adverse events, compared with controls. These studies, however, were performed by a single experienced center with a very skilled team and enrolled predominantly patients with ischemic cardiomyopathy, a large majority of whom were not receiving β-blockers. All of these factors were recognized as limitations.

The ELVD-CHF study was performed in 15 unselected cardiac rehabilitation centers throughout Italy that simply agreed to take part in the trial and to adopt the exercise protocol. This better reflects the standard application of exercise therapy to CHF in the community, and the results attained thus favor the widespread practice of ET as an adjunct to optimal medical therapy. Indeed, in line with other supervised studies conducted at a single center, we found an improvement in exercise capacity and quality of life and a trend toward a lower rate of hospital readmission for temporary worsening dyspnea in the training group, in the absence of other major adverse cardiac events.

The proportion of patients taking β-blockers, predominantly carvedilol, was higher than in previous studies and equally distributed in the 2 groups. Nevertheless, the potential for an additional benefit of ET over β-blockers remains to be clearly demonstrated. Therefore, an accurate assessment of the effects of ET in CHF patients systematically treated with β-blockers requires further studies.

Study Limitations

Our study involved relatively young patients (mean age, 60 years), predominantly men, with stable CHF (clinical stability for ≥3 months before entry into the study). Thus, the results may not be applicable to all elderly patients or to patients with recent decompensated congestive heart failure.

A moderate ET program (60% of peak $\dot{V}_{O_2}$) was adopted. Whether similar results may be obtained with different intensities of ET remains to be established.

Conclusions

This randomized, controlled study demonstrates that long-term moderate ET attenuates abnormal remodeling in patients with stable CHF caused by severe LV systolic dysfunction. We confirm that ET is safe and improves functional capacity and quality of life. The endorsement of the antiremodeling

effect in a multicenter trial underlines that ET should be considered in the treatment algorithm of CHF as a highly cost-effective resource in an increasingly competitive health-care system.

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