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Long-term versus intermediate-term supervised exercise training in advanced heart failure: Effects on exercise tolerance and mortality

Alexander Tenenbaum [a,1], Dov Freimark [b,1], Ella Ahron [b], Nira Koren-Morag [a], Ehud Schwamenthal [a], Enrique Z. Fisman [a], Michael Shechter [b], David Tanne [c], Dvora Kachlon [a], Michael Motro [a], Yehuda Adler [a,*]

[a] *Cardiac Rehabilitation Institute, Chaim Sheba Medical Center, Tel-Hashomer, and the Sackler Faculty of Medicine, Tel-Aviv University, 52621 Tel-Hashomer, Israel*

[b] *Heart Failure Center, Chaim Sheba Medical Center, Tel-Hashomer, and the Sackler Faculty of Medicine, Tel-Aviv University, Israel*

[c] *The Stroke Unit, Department of Neurology, Chaim Sheba Medical Center, Tel-Hashomer, and the Sackler Faculty of Medicine, Tel-Aviv University, Israel*

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Abstract

Aim: To date there have been no studies exploring the effects of long-term versus intermediate-term and short-term supervised exercise training program in patients with severe chronic heart failure (CHF) on optimal medical therapy. We assessed exercise tolerance and mortality in CHF patients undergoing long- versus intermediate-term exercise training (ET).

Methods: Forty-two consecutive severe CHF patients (New York Heart Association functional class III) were referred for a supervised exercise and cardiac rehabilitation program and were followed-up for 3 years: 20/42 (48%) patients discontinued ET after intermediate-term period of 1.6±0.8 years (Group A, intermediate-term ET), and 22/42 (52%) remained on the ET program for 3.0±0.3 years (Group B, long-term ET). Exercise duration, 6-min walked distance and metabolic equivalents (METs) assessed by modified Bruce protocol were recorded before, 4.5 months after, and 3 years after initiation of ET.

Results: Both groups were comparable regarding age, gender, prevalence of ischemic etiology, mean ejection fraction and medications. Risk factors for ischemic heart disease were similar, except for the prevalence of diabetes, which was higher in Group A compared to Group B (11/20 versus 5/22, $p=0.03$). Significantly more Group A patients died after ET discontinuation (4/20 versus 0/22, $p=0.01$). At the end of follow-up a significant improvement could be seen in Group B patients compared to A in exercise duration, 6-min walked distance and metabolic equivalents ($p<0.01$ for all).

Conclusions: Higher survival rate was observed in severe CHF patients undergoing long-term versus intermediate-term exercise training. Long-term supervised exercise training is safe and improves exercise tolerance in these patients.

Keywords: Heart failure; Exercise; Functional capacity; Rehabilitation; Mortality

Congestive heart failure (CHF) represents a prevalent health problem throughout the world. Despite considerable advances in the diagnosis and medical treatment of CHF, this condition is associated with high rates of morbidity and mortality and it is responsible for numerous hospitalizations. Reduced exercise tolerance in patients with CHF results in progressive functional deterioration. Exercise training has been shown to have a positive impact both on the course of the disease and its outcome on CHF patients [1–16]. To date, however, there have been no studies exploring the effects of long-term versus intermediate-term and short-term supervised exercise training program in patients with severe CHF on optimal medical therapy [17]. This study was aimed to compare survival and exercise tolerance in advanced

* Corresponding author. Tel.: +972 3 5305208; fax: +972 3 5303084.
E-mail address: yadler@sheba.health.gov.il (Y. Adler).

[1] The first 2 authors contributed equally to this work.

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CHF patients undergoing intermediate versus long-term rehabilitation programs.

1. Methods

1.1. Study design and population

The initial study cohort comprised 44 consecutive severe CHF patients (New York Heart Association functional class III) who were referred for a government-sponsored supervised exercise training (ET) and cardiac rehabilitation program (Fig. 1). All patients were in a stable condition and in absence of hospitalizations before the beginning of the study during 3 months at least. Two patients died during short-term (4.5 months) exercise training period and were excluded from the analyses. Forty-two remained patients were on our outpatient clinic-based optimal medical treatment and followed-up for 3 years: 20/42 (48%) following economic considerations or travel issues voluntarily discontinued ET after mean 1.6±0.8 years; they comprised Group A (*intermediate-term ET*). The remained 22/42 (52%) patients continued the ET program for the additional long-term period till end of the study (mean follow-up 3.0±0.3 years); they comprised Group B (*long-term ET*). For Group A the mean period without ET till the end of the study comprised 1.5±0.9 years. After enrollment in the study, all patients underwent hemodynamics and exercise test examination. Survived patients from both groups repeated the same tests 4.5 months after (short-term ET period) and 3 years after initiation of ET. The last (third) hemodynamics and exercise test examination was considered as the end of the study. The patients have joined the rehabilitation program between January 2000 and February 2001. The third test, that represents the end point of the research, was performed between June and August 2003. Two patients from Group A missed last hemodynamics and exercise test examination; 3 patients who underwent cardiac transplantation during follow-up (1 from Group A and 2 from Group B) were excluded from the last examination.

Inclusion criteria included CHF $\geq$ 6 months and no change in concomitant medications for $\geq$6 weeks. Exclusion criteria included severe lung disease, severe valvular disease, exertional angina, symptomatic peripheral vascular disease, diabetes with severe end-organ damage, significant and disabling cerebrovascular disease, malignancies, history of drug and/or alcohol abuse. All patients received detailed diet advice in the form of initial 15-min individual session. During follow-up regular additional reinforcements of dietary advice were performed. The institutional review board (Helsinki Committee) approved the study and all participants signed written informed consent forms.

1.2. Noninvasive resting and exercise hemodynamics

We used thoracic electrical bioimpedance (TEB) technology for noninvasive evaluation of hemodynamic parameters [18]. TEB technology is based on Ohms law, which states that resistance (impedance or Z) to alternating current flow is inversely proportional to voltage (U) when the current (I) remains constant ($Z=U/I$). Changes in impedance (delta Z or dZ) over changes in time (delta t or dt), when current is held constant, reflect a change in the properties of the conducting medium (inherent resistance, length or cross-sectional area). TEB utilizes 4 sensors placed at the neck and thorax to transmit a 2.5 mA, 70 kHz signal and offers a simple, convenient noninvasive method of determining hemodynamic parameters including stroke index (SI), cardiac index (CI), and systemic vascular resistance (SVR). SI, CI and SVR were determined using

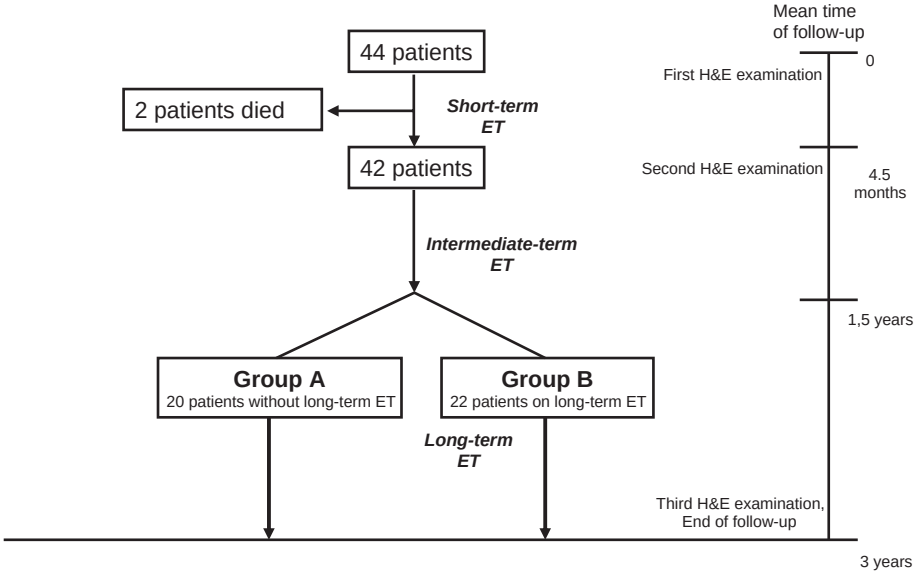

Fig. 1. Patients flow chart. ET—exercise training; H&E examination—hemodynamics and exercise test examination.

the commercial available TEB device (BioZ, Cardiodynamics, San Diego, CA).

1.3. Exercise protocol

All patients underwent a 6-min walk test, cardiopulmonary exercise testing (on baseline only), and a graded exercise test using modified Bruce protocol. The exercise test (Bruce protocol) and the 6-min walk distance test were performed on different days, but in the same week for all the participants. After concluding baseline tests, the exercise group patients were enrolled in a supervised exercise and rehabilitation program, which included a 15-min warm-up period, followed by 45 min of exercise on a treadmill, a stair machine, and a bicycle at 60–70% of maximal heart rate. Exercise was performed twice a week; compliance was monitored, and the exercise prescription was adjusted if maximal exercise capacity was improved.

1.4. Statistical analysis

Results were expressed as mean values±S.D. for continuous variables and as frequency and percentage for categorical variables. Comparison of categorical characteristics was performed by chi-square analysis and fisher's exact test. Continuous variables were compared using Analysis of Variance (ANOVA). ANOVA with repeated measures was applied to assess the effect of exercise training as well as the interaction between group and effect. A p value of <0.05 was considered significant.

2. Results

No significant differences were found between the two study groups regarding age, gender, prevalence of ischemic etiology, coronary artery disease (CAD), proportion of heart transplantation candidates, history of open-heart surgery and stroke. Risk factors for ischemic heart disease were similar in prevalence in both groups, except for diabetes, which was significantly more common in Group A compared to Group B (Table 1). The most common underline etiology of CHF in the two study groups was ischemic heart disease (Table 2). There were no significant differences between the groups in the proportion of patients receiving all types of cardiovascular drugs (Table 3). Furosemide (100% of patients), angiotensin converting enzyme (ACE) inhibitors, beta-blockers and aspirin were the most commonly used medications.

No significant differences were found between the two study groups with regard to the baseline exercise and hemodynamic parameters (Table 4). Mean left ventricular ejection fraction and peak VO2 were low and similar in both groups: respectively 24±6% versus 25±6% and 12.0±3.5 ml/kg/min versus 11.4±3.7 ml/kg/min (Group A versus B).

After 18 weeks (4.5 months) of joint short-term exercise training, functional parameters improved significantly in both groups: in Group A mean exercise test duration increased by 73% (Fig. 2, panel A, $p<0.01$), 6-min walked distance increased by 47% (Fig. 2, panel B, $p<0.01$) and mean METs achieved during exercise test increased by 58% ($p<0.01$), in Group B mean exercise test duration increased by 76% ($p<0.01$), 6-min walked distance increased by 44% ($p<0.01$) and mean METs achieved during exercise test

Table 1
Baseline clinical characteristics of study population

Characteristics	Group A ($n=20$)	Group B ($n=22$)	p
Age (years)	62.5±12	60.7±15	0.685
Male gender	17 (85%)	17 (77%)	0.406
BMI (kg/m^2)	27.2±4	26.3±4	0.473
Hypertension	10 (50%)	11 (50%)	0.621
CRF	5 (25%)	6 (27%)	0.574
Diabetes	11 (55%)	5 (23%)	0.033
Hyperlipidemia	13 (65%)	16 (73%)	0.418
Smoking	9 (45%)	12 (55%)	0.379
Alcohol use	1 (5%)	2 (9%)	0.537
Prior MI	17 (85%)	14 (64%)	0.110
Prior CABG	8 (40%)	4 (18%)	0.111
Stroke	4 (20%)	1 (5%)	0.144
Pacemaker	3 (15%)	4 (18%)	0.556
AICD	2 (10%)	2 (9%)	0.659

Values are expressed as number (%) or mean±S.D. BMI—body mass index; CABG—coronary artery bypass grafts; MI—myocardial infarction; CRF—chronic renal failure; AICD—automatic implantable cardioverter-defibrillator.

Table 2
Underline etiology of congestive heart failure for both study groups

Etiology	Group B ($n=22$)	Group A ($n=20$)	p value
Ischemic heart disease	16 (80%)	14 (64%)	0.239
Idiopathic dilated cardiomyopathy	3 (15%)	4 (18%)	0.262
Valvular (non-rheumatic) disease	0	1 (4.5%)	0.309
Alcoholic cardiomyopathy	1 (5%)	0	0.305
Postpartum cardiomyopathy	0	2 (9%)	0.140
Rheumatic heart disease	0	1 (4.5%)	0.309

Table 3
Distribution of cardiovascular drugs among the study patients

Drug	Intermediate-term	Long-term	p
Oral hypoglycemics	8 (40%)	3 (14%)	0.550
Anticoagulants	8 (40%)	10 (46%)	0.483
Aspirin	15 (75%)	14 (64%)	0.323
Aldactone	7 (35%)	7 (32%)	0.543
Thiazides	1 (5%)	3 (14%)	0.341
Furosemide	20 (100%)	22 (100%)	1
Digoxin	11 (55%)	14 (64%)	0.399
Nitrites	12 (60%)	9 (41%)	0.177
Alpha-blockers	9 (45%)	8 (36%)	0.399
Beta-blockers	12 (60%)	16 (73%)	0.293
ACE-inhibitors	18 (90%)	22 (100%)	0.8
Antiarrythmics	2 (10%)	5 (23%)	0.247

ACE-inhibitors: angiotensin converting enzyme (ACE) inhibitors.

Table 4
Baseline exercise and hemodynamic parameters of study participants

Parameters	Group A ($n=20$)	Group B ($n=22$)
Exercise duration (min)	5.9±3.9	5.7±3.6
6-min walked distance (m)	308±113	307±80
Metabolic equivalents (METs)	3.8±2.1	3.6±1.9
Heart rate (bpm)	79±18	77±12
SI (ml/m^2)	40.3±12.1	38.0±10.6
CI (l/min/m^2)	2.5±0.4	2.7±0.3
SVR (dyne s/cm^5)	1398±448	1236±232
Double product	16,276±4209	16,524±4485
Ejection fraction	24±6	25±6
Peak VO2 (ml/kg/min)	12.0±3.5	11.4±3.7

Values are mean±S.D.; CI=cardiac index; SI=stroke index; SVR=systemic vascular resistance; all differences are non-significant.

increased by 59% ($p<0.01$). After discontinuation of exercise training in Group A mean exercise test duration decreased by 27%, 6-min walked distance decreased by 28% and mean METs achieved during exercise test decreased by 30% during follow-up. In contrast, in Group B mean exercise test duration increased by 13%, 6-min walked distance also increased by 13% and mean METs achieved during exercise test increased by 16% additionally during long-term exercise training (p for trend < 0.001).

Similar to exercise characteristics, main hemodynamic parameters (post peak CI and SVR) improved significantly in both groups after 18 weeks of joint short-term exercise training, but the opposite trends were observed during further follow-up after discontinuation of exercise training in Group A (Fig. 3, panels A and B).

Four patients (20%) from Group A died during years of follow-up (1 diabetic patient died from sudden cardiac death at home and 3 non-diabetic patients died from worsening of CHF at hospital), whereas in Group B all patients survived this period (Fig. 4, $p=0.01$).

3. Discussion

Our study demonstrates that a long-term (3 years) supervised exercise and rehabilitation program significantly improves exercise tolerance and survival in severe (NYHA class III) CHF patients. After initial period of joint short-term exercise training, functional parameters improved in both groups, but decreased significantly after discontinuation of exercise training in Group A. Moreover, patients, who gave up rehabilitation program and comprise Group A, showed a worse survival as compared to patients who continued exercise training. Probably, continuation of exercise training, but not its duration might be imperative for better outcome. The answer on this unresolved question remains to be determined in randomized study with an appropriate statistical power.

CHF is a major health hazard, which is increasing to epidemic proportions, while placing a heavy financial and social burden on public health funding [19–22]. Although medical and/or technological interventions can be beneficial to the heart failure patient, their effect on exercise intolerance, a major symptomatic limiting factor associated with reduced quality-of-life, is less convincing [20].

Recent data have demonstrated that exercise training can improve central hemodynamics and peripheral abnormalities (endothelial dysfunction and skeletal myopathy), which characterize the progression of the syndrome [23–25]. Advanced CHF is characterized by activation of different neurohormonal mechanisms, including enhancement of rennin–angiotensin system, elevation of circulating catecholamines, natriuretic peptides and arginine–vasopressin. Physical training has been demonstrated to decrease rest plasma catecholamine levels in patients with ischemic heart disease and reduced left ventricular function [26–29]. Moreover, physical training seems to beneficially modulate peripheral immune responses of CHF expressed by elevated circulating proinflammatory cytokines, soluble cellular adhesion molecules and soluble apoptosis signaling molecules, resulting in improvement in exercise capacity of CHF patients [24].

In the current study, although patients with severe CHF from both groups had similar reduced baseline exercise tolerance and hemodynamic parameters, a supervised hospital-based exercise and rehabilitation program signifi-

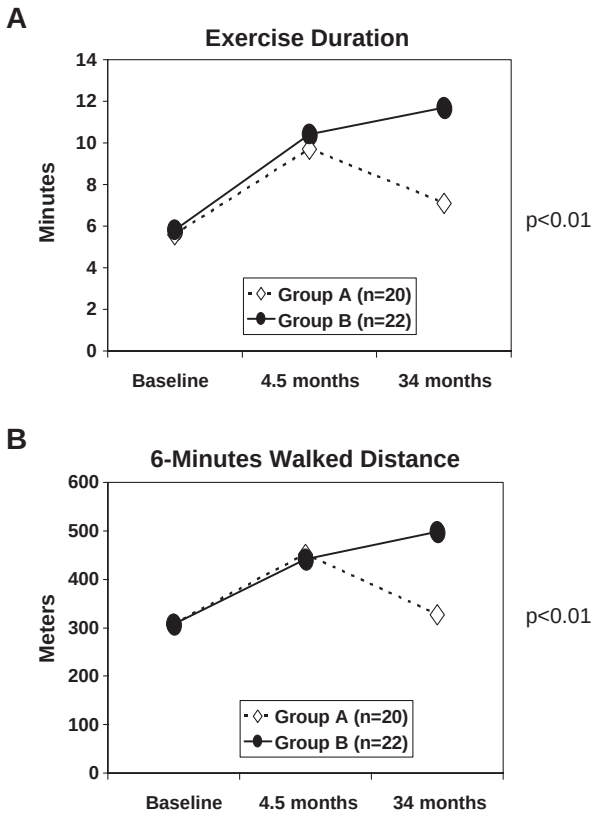

Fig. 2. Changes in exercise duration (panel A) and 6-min walked distance (panel B) throughout the study period: intermediate-term exercise training (ET), Group A versus long-term ET, Group B. Each data point represents the mean value for all participants who remained in follow-up at that time.

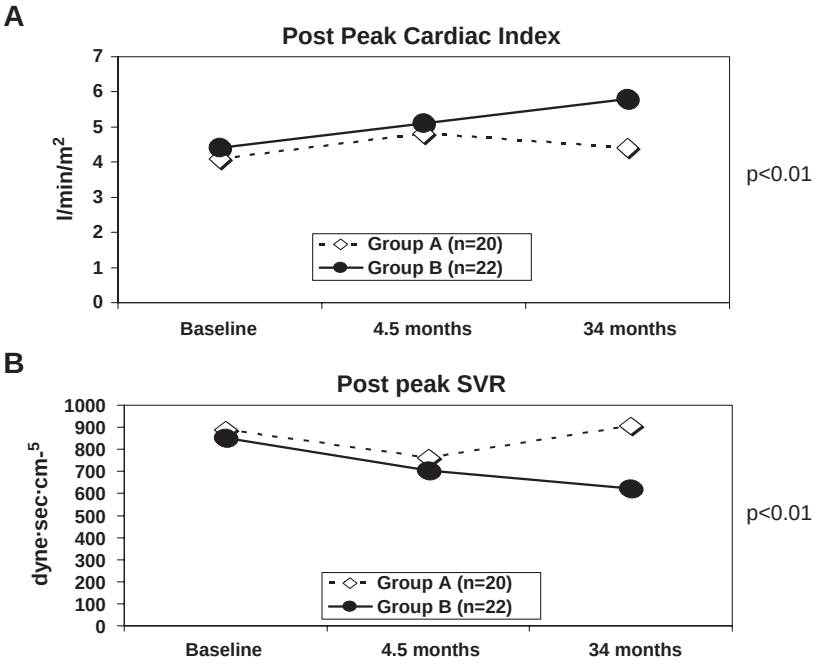

Fig. 3. Changes in post peak cardiac index (panel A) and post peak systemic vascular resistance (SVR, panel B) throughout the study period (intermediate-term ET, Group A versus long-term ET, Group B).

cantly increased exercise tolerance, assessed by exercise duration time and METs achieved during exercise test. The data regarding mortality which were observed in our study emphasize the possible role of long-term exercise training in improving the survival of these patients even in the presence of optimal currently available drug therapy. These findings are in line with those of the European Heart Failure Training Group [30] and others [4,17].

Our study revealed that supervised physical training in severe CHF patients is safe. The program devised for these severely ill subjects involved an aerobic exercise, which was not substantially less vigorous than a program designed for less severely ill patients, and included dynamic endurance training, as well as static training sessions. The sessions were held twice a week, with no specific instructions to exercise at home and a high level of attendance was achieved, despite the fact that the training sessions were twice weekly. To date, no consensus has been reached regarding the optimal exercise protocol for these patients. The protocol used in the current study was similar to a number of previous exercise training studies [5,31] although less vigorous than others [26,32].

The results of our study are in concordance with the relatively low adverse event rate reported from exercise

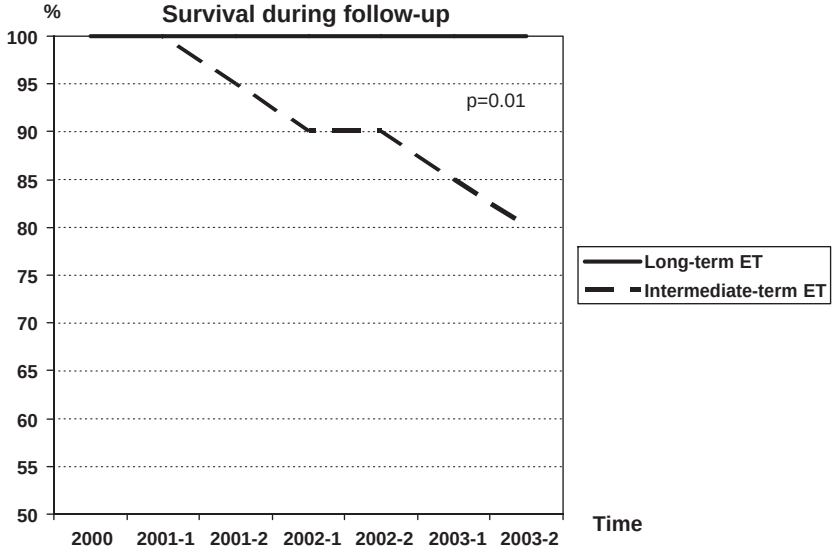

Fig. 4. Survival curves for the study groups (intermediate-term ET, Group A versus long-term ET, Group B, half-year increment for time axis).

training studies conducted in CHF patients [17,30], and may assist the ACC/AHA and ESC in encouraging severe (NYHA class III) CHF patients to participate in supervised exercise and rehabilitation programs.

3.1. Study limitations

Our study has several important limitations.

The current trial was not a randomized trial. Instead, the control group represented patients who voluntarily discontinued ET due to reimbursement or travel issues. Therefore, a potential for referral and enrollment bias exists, although patients from both study groups had similar baseline characteristics and medications except the prevalence of diabetes, which was higher in Group A. The data regarding hospitalizations were not available. Cardiopulmonary exercise testing was performed only on baseline. Therefore, caution should be used in interpreting our findings identified in relatively small groups of patients without randomization.

3.2. Conclusion

Higher survival rate was observed in severe CHF patients undergoing long-term versus intermediate-term exercise training. Long-term supervised exercise training is safe and improves exercise tolerance in these patients.

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