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Original Scientific Paper

Effects of a 14-month low-cost maintenance training program in patients with chronic systolic heart failure: a randomized study

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Background **Exercise training is known to be beneficial in chronic heart failure (CHF) patients but there is a lack of studies following patient groups for longer duration with maintenance training programs to defer deconditioning.**

Methods **Study base consisted of all patients diagnosed with CHF in a 3-year period. Sixty-six patients with systolic CHF (ejection fraction <45, New York Heart Association II–III) were randomized to 12 months of either usual care or home-based maintenance exercise with group training sessions every 2 weeks after an initial 8-week training program. The primary endpoint was maximum workload; secondary endpoints were 6-min walk test, incremental shuttle walk test, sit-to-stand test, quality of life, and serological markers.**

Results **Six patients died and 43 completed the study. The initial 8-week training was associated with small but significant improvement in all of the functional tests. In both groups there was a significant decline in the maximum workload the next 12 months ($P=0.03$ and $P<0.001$, respectively) but after an adjustment for difference between groups in baseline characteristics, maintenance intervention reduced the decline in the maximum workload by 8.0 W (95% CI: 3.0–13.0, $P=0.002$). No effect of maintenance intervention was observed for 6-min walk test, incremental shuttle walk test, sit-to-stand test, or quality of life. After 14 months changes in most markers of inflammation, endothelial damage, and glycemic control were more beneficial in the intervention group.**

Conclusion **A low-cost maintenance intervention in CHF patients reduced the decline in the maximum workload compared with usual care but not in other measures of physical function. Results suggest beneficial effects of long-term maintenance training on glycemic control, inflammation, and endothelial function.** ***Eur J Cardiovasc Prev Rehabil*** **16:430–437 © 2009 The European Society of Cardiology**

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Keywords: exercise training, glycemic control, heart failure, inflammation

Introduction

There are abundant studies showing that patients with chronic heart failure (CHF) benefit from short-term exercise training with improvement in physiologic measurements, such as peak oxygen consumption (VO_2-max), autonomic function, plasma norepinephrine levels, inflammatory markers, endothelial function, functional capacity [e.g. 6-min walk test (6MWT)], and quality of life measures [1–6]. However, the beneficial effects of exercise training are rapidly lost after termination of training in enthusiastic protocols [7] and means of improving long-term effects are needed.

Most studies of exercise training have been based on supervised training sessions, either hospital-based or residential programs, conducted on highly selected groups of primarily younger males with no or only slight comorbidity [1]. This raises the question of whether

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these findings can be transferred to a general clinical population, which is older and has high prevalence of comorbidity. In addition, most of the evidence is based on costly training programs that are not available to most CHF patients, in particular not as maintenance programs. Home-based exercise training programs are less costly and would be more broadly applicable to nonselected patients. Unfortunately, results from home-based exercise programs have been conflicting [8–11], perhaps partly because of insufficient training intensities and low adherence rates.

Home-based training combined with intermittent, supervised group-based training sessions to keep the patients motivated and increase adherence, and continuous adjustment of training intensity may address some of these needs. The aim of this randomized trial consecutively including all eligible patients with CHF was thus to determine whether a low-budget 12-month home-based maintenance training program could defer deconditioning.

Methods

Patient selection

All patients in the outpatient clinic or discharged from hospital with a diagnosis of CHF from 1 January 2002 to 31 January 2005 were screened for inclusion criteria: left ventricular ejection fraction (LVEF) $\leq 45\%$ assessed by a recent echocardiography (< 6 months); New York Heart Association (NYHA) functional class II–IV; and optimal medical treatment. Exclusion criteria were: severe valvular heart disease; musculoskeletal impairment impeding training; other chronic disease with expected shortened life span; ischemia or angina pectoris at low strain (≤ 45 W), or malignant cardiac arrhythmias (> 3 consecutive ventricular extrasystoles, ventricular tachycardia or supraventricular tachycardia with ventricular action of > 150 bpm) during baseline cycle ergometer testing; or myocardial infarction in the last 8 weeks. Randomization was performed at the Copenhagen Trial Unit (*http://ctu.rh.dk*) after stratification according to NYHA functional class (II vs. III–IV) and age (70 or below vs. above 70).

Patient assessment

Background data included medical history, socioeconomic data, risk factors, and symptoms. Assessment at baseline, 8 weeks, and 14 months consisted of exercise testing, functional tests, anthropometric data, and biochemical characteristics. Complete data are not available on dropouts.

The exercise test was a maximal symptom limited-cycle ergometer test with a standardized protocol of a workload of 25 W increasing the intensity every 2 min by 10 W until physical exhaustion. Further functional tests were 6MWT, incremental shuttle walk test (ISWT), and sit-to-stand test (STS). As home-based walking with calibration of walking speed was central to the maintenance intervention, we included the ISWT that has good reproducibility and close correlation to VO_2max and also predicts event-free survival in patients with CHF [12–15]. In brief, this test was carried out on a 10 m track with patients instructed to walk at a pace following a signal on a tape recorder while increasing speed by 10 m/min every minute. The patient continues walking until not able to reach the next cone in time for the signal or until exhaustion. The total distance walked is the main outcome of the test. The test allows estimation of VO_2max and a walking speed correlating to the desired percentage (70–80%) is calculated. This speed was then tested to ensure that the patient walked at the correct speed for home-based training.

Muscle strength was measured by STS previously validated in elderly persons [16]. Patients were instructed to get up and sit down as many times as possible within 30 s using the chair's armrests.

Exercise training

All patients received 8 weeks of supervised training twice weekly in hospital-based rehabilitation facilities. Each supervised 1.5-h training session comprised of 20 min warm-up period followed by four 6-min series of aerobic training (walking, cycling, step machine, and step board) and two posts of resistance endurance exercises (leg press and exercises with rubber bands for quadriceps, gluteus/hamstring region, and arms; three sets of 20 repetitions with each arm/leg). Each patient's training intensity was adjusted to achieve 70–80% of peak oxygen consumption, corresponding to 4–5 on the Modified Borg Scale [range 0 (no breathlessness at all) to 10 (maximal breathlessness)]. Training intensity and resistance was continually adjusted to the desired level. Patients were encouraged to walk or do other physical training for 20–30 min each day at home at a similar level of exertion. They were also given rubber bands for resistance training exercises at home on a daily basis.

After the initial 8 weeks, the patients randomized to the intervention group continued supervised exercise sessions as described above every 2 weeks for an additional 12 months and were encouraged to exercise at home. A training diary was kept by each patient and presented at the group sessions. The patients randomized to usual care were encouraged to keep on training at home but were not offered group sessions or to keep diaries.

Statistical analysis

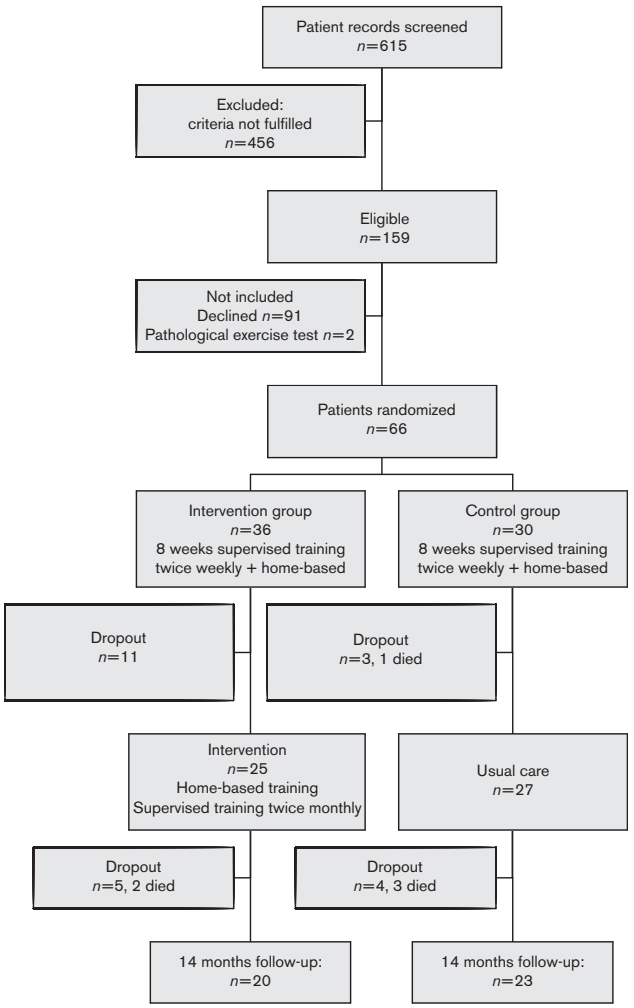
Groups were compared with two-sided χ^2 statistics and unpaired t-tests to evaluate differences in baseline characteristics and changes between the two groups. Changes within groups were compared by paired t-tests. Predictors of change in maximum workload during the study period adjusting for baseline differences between

groups were determined by analysis of variance and multivariate linear regression analyses. A P value of less than 0.05 was considered statistically significant. All statistical analyses were performed in STATA 10.0 (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, Texas, USA).

Results

The flow chart (Fig. 1) summarizes the screening and inclusion procedure. Major reasons for exclusion were LVEF greater than 45, musculoskeletal disability, dementia, lack of symptoms, and death before screening. Two patients were excluded because of pathological exercise tests (one because of arrhythmia and one because of angina at low workload), leaving 66 patients for randomization. Six patients died during the study and 43 patients completed. The 23 dropouts did not differ from the completers regarding sex, age, socioeconomic factors, or severity of CHF (assessed by LVEF and NYHA classification) but significantly more dropouts had comorbidity (74 vs. 48%, $P = 0.05$). The dropouts also had poorer functional tests at baseline for maximum workload ($P = 0.05$), 6MWT ($P = 0.02$), and ISWT ($P = 0.02$).

Fig. 1



Flow chart. All patients with a diagnosis of chronic heart failure from 1 January 2002 to 31 January 2005 consecutively screened for inclusion.

Table 1 shows baseline characteristics of patients in the two groups. No differences were observed between groups in etiology of CHF, earlier revascularization procedures, angina, or number of patients with pacemaker/implantable cardioverter defibrillators. Patients were under optimal medical treatment.

In response to the initial 8 weeks of training, patients' maximum work load, exercise time, STS, ISWT, and 6MWT improved significantly (results not shown). However, at 14 months there was a significant deterioration in the maximum workload and exercise time in the intervention and the usual care group (Table 2), a continued significant increase in STS and no change in the ISWT or the 6MWT.

The change from baseline exercise capacity to the end of the maintenance program was −5.5 (2.4) W for the intervention group and −10.9 (2.2) W for the usual care group (Fig. 2) (P for difference between groups 0.06).

Table 1 Baseline characteristics of patients in the intervention and the usual care group

	Maintenance training $n=20$	Usual care $n=23$	P
Women	4 (20%)	5 (22%)	0.89
Age	68.0 ± 11.0	66.9 ± 12.5	0.76
Clinical characterization			
LVEF	33.8 ± 9.5	28.9 ± 9.6	0.10
NYHA functional class III–IV	5 (25%)	3 (13%)	0.32
Medications			
ACE-inhibitor or ARB	20 (100%)	22 (95%)	0.35
β-blockers	18 (90%)	21 (91%)	0.88
Spironolactone	2 (10%)	9 (39%)	0.03
Diuretics	13 (65%)	20 (87%)	0.09
Statins	17 (85%)	17 (74%)	0.58
Digoxin	5 (25%)	9 (39%)	0.32
CVD risk factors			
BMI (kg/m^2)	27.7 ± 4.12	27.7 ± 5.92	0.89
Current smoker	1 (5%)	6 (26%)	0.06
Alcohol (units/week)	7.8 ± 15.6	8.1 ± 7.5	0.92
Systolic blood pressure (mmHg)	124.8 ± 19.0	123.1 ± 20.2	0.78
Comorbidity			
COPD	3 (15%)	2 (8.7%)	0.52
Diabetes	4 (20%)	7 (30%)	0.43
Functional tests			
Max workload (W)	93.5 ± 37.7	97.2 ± 36.1	0.63
Exercise time (s)	875.4 ± 441.7	905.5 ± 435.5	0.59
STS test (n per 30 s)	12.2 ± 3.7	13.1 ± 4.2	0.78
ISWT (m)	363.5 ± 231.9	392 ± 187.4	0.67
6MWT (m)	437.8 ± 125.5	476.7 ± 106.8	0.86

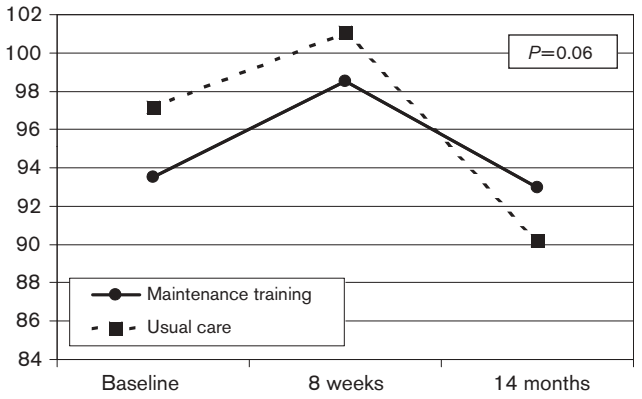
Values are given as mean ± SD or number (%). 6MWT, 6-minute walk test; ACE, angiotensin I converting enzyme; ARB, angiotensin-receptor blocker; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ISWT, incremental shuttle walk-test; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS, sit-to-stand.

Table 2 Comparison of functional tests before and after maintenance training program by intervention group

	Maintenance training $n=20$			Usual care $n=23$			Between groups
	8 weeks	14 months	*P*	8 weeks	14 months	*P*	*P*
Max workload (W)	98.5 ± 9.1	93.0 ± 8.3	0.03	101.1 ± 7.6	90.2 ± 6.6	<0.0001	0.06
Exercise time (sec)	928.6 ± 107.8	863.4 ± 98.7	0.03	965.0 ± 93.0	840.6 ± 82.6	<0.0001	0.10
STS test (*n* per 30 s)	14.0 ± 0.8	15.9 ± 1.1	0.05	14.9 ± 0.8	16.3 ± 1.0	0.0048	0.61
ISWT (m)	408.4 ± 62.8	385.3 ± 61.9	0.22	402.6 ± 35.2	378.3 ± 37.4	0.19	0.96
6-MWT (m)	465.5 ± 29.7	448.9 ± 29.7	0.11	490.7 ± 20.5	475.9 ± 24.2	0.12	0.89

Values are mean ± SE. 6MWT, 6-min walk test; ISWT, incremental shuttle walk-test; STS, sit-to-stand.

Fig. 2



Maximum symptom limited exercise capacity at baseline, 8 weeks and 14 months in the maintenance intervention group and usual care group. Both groups completed an initial 8-week training program with training sessions twice weekly where after only the maintenance group continued with structured training sessions. *P* value for difference between groups changing from baseline to 14 months.

The decline in the maximum workload, however, was correlated to baseline exercise capacity, LVEF, Canadian Cardiovascular Society class, BMI, and history of hypertension and a multivariate linear regression analysis with change in the maximum workload from 8 weeks to 14 months as the dependent variable adjusting for these parameters yielded the results shown in Table 3. The maintenance intervention was associated with a significantly better maximum workload with a difference between groups of 8.0 W (95% CI: 3.0–13.0). Results also indicated that better maximum workload at eight weeks better LVEF, more angina, higher BMI, and a history of hypertension were associated with loss of exercise capacity during the maintenance period. Sex, age, systolic blood pressure, diabetes or other comorbidity, baseline *N*-terminal Pro-B-type natriuretic peptide (NT-proBNP), and adherence to the group-based training sessions were not significantly associated with the change. For the remaining functional tests (STS, ISWT, and 6MWT) there were no differences between groups.

The metabolic markers indicated better metabolic fitness in the intervention group, as evidenced by HbA1c and plasma glucose without significant changes in insulin

Table 3 Results from multivariate linear regression analyses with change in maximum exercise capacity during the maintenance period from 8 weeks to 14 months as dependent variable

	Coefficient	95% CI	*P*
Intervention (training vs. usual care)	8.0	3.0–13.0	0.002
Maximum workload 8 weeks (per 10 W)	−1.0	−1.7 to −0.3	0.006
LVEF (LVEF < 30 vs. ≥ 30)	8.9	2.9–14.8	0.005
Angina (CCS 2 vs. 0/1)	−15.30	−25.8 to −4.8	0.006
BMI (BMI < 30 vs. ≥ 30)	7.1	0.6–13.7	0.006
History of hypertension (yes vs. no)	−7.7	−12.9 to 0.2.4	0.03

Positive values represent increase in exercise capacity. CCS, Canadian Cardiovascular Society class; CI, confidence interval; LVEF, left ventricular ejection fraction.

(Table 4). Furthermore, plasma free fatty acid (FFA) and glycerol concentrations decreased, which indicates that lipolysis was diminished in response to maintenance training. For the inflammatory markers, the change was significantly more beneficial for high-sensitive C-reactive protein in the maintenance intervention versus the usual care group, whereas for orosomucoid, urine-orosomucoid, and urine-albumin creatinin ratio, the differences were of borderline significance. The maintenance program did not affect concentrations of plasma homocystein, lipids, cortisol, epinephrine, insulin-like growth factor, or NT-proBNP.

Discussion

A small but significant increase was observed in functional capacity after 8 weeks of training, but after 12 months of maintenance intervention there was a significant reduction in the maximum workload and exercise time in both groups. Thus, the intervention failed to reach the desired goal of maintaining the physical fitness achieved after a short training program. Only a few randomized controlled studies of exercise training of patients with CHF with prolonged follow-up have addressed the question of how to maintain training effects in nonselected patient groups. In a comprehensive review from 2004, two studies with duration of intervention of more than 6 months were identified [1]. In the study by Belardinelli *et al.* [17], 94 patients (LVEF ≤ 40, NYHA II–IV) were randomized to 14 months of training versus usual care. A highly significant effect of intervention on peak oxygen uptake, resting heart rate, thallium uptake, and quality of life was observed. This is the only study to date to show significantly reduced risk of

Table 4 Change in serological markers between 8 weeks and 14 months in the maintenance intervention and usual care groups

	Intervention $n=20$			Usual care $n=23$			
	8 weeks	14 months	Change	8 weeks	14 months	Change	P^a
Metabolic markers							
HbA_1c (%)	6.3 ± 0.2	6.3 ± 0.1	0.03 ± 0.1	6.5 ± 0.3	6.9 ± 0.4	0.4 ± 0.1	0.03
Glucose (mmol/l)	6.0 ± 0.2	6.0 ± 0.2	− 0.1 ± 0.2	6.6 ± 0.7	7.2 ± 0.7	0.6 ± 0.3	0.05
Insulin (pmol/l)	74.6 ± 14.3	72.5 ± 13.4	− 2.1 ± 9.8	57.7 ± 11.5	67.2 ± 10.0	9.5 ± 9.8	0.41
Glycerol (μmol/l)	124.3 ± 11.3	110.8 ± 11.0	− 13.5 ± 13.4	111.3 ± 9.6	138.9 ± 11.7	27.5 ± 11.6	0.02
Free fatty acids (μmol/l)	288.0 ± 40.6	245.0 ± 27.9	− 43.0 ± 52.6	279.5 ± 36.5	376.8 ± 54.1	97.3 ± 50.1	0.06
Inflammatory markers							
hsCRP (mg/l)	6.5 ± 2.5	2.7 ± 0.7	− 3.7 ± 2.5	5.4 ± 1.8	10.0 ± 4.6	4.6 ± 3.1	0.05
Orosomucoid (g/l × 10)	9.5 ± 0.7	8.0 ± 0.4	− 1.5 ± 0.5	9.4 ± 0.6	9.0 ± 0.8	− 0.4 ± 0.4	0.10
Interleukin 6 (ng/l)	20.5 ± 5.4	17.3 ± 4.0	− 3.2 ± 2.0	41.6 ± 14.6	48.3 ± 15.7	6.7 ± 6.9	0.22
TNF-α (ng/l)	7.5 ± 1.5	8.5 ± 1.7	1.1 ± 0.7	9.2 ± 1.9	9.0 ± 2.0	− 0.1 ± 0.4	0.13
U-orosomucoid (mg/l)	13.1 ± 4.8	10.9 ± 4.0	− 2.1 ± 3.5	6.4 ± 2.5	13.6 ± 4.8	7.2 ± 3.6	0.07
U-alb/creatinin (mg/mmol)	7.9 ± 3.4	6.6 ± 2.1	− 1.4 ± 1.7	8.1 ± 5.4	10.4 ± 6.1	2.4 ± 1.1	0.06
Other serological markers							
Homocystein (umol/l)	14.5 ± 1.1	14.5 ± 1.2	− 0.1 ± 0.6	15.8 ± 1.1	16.1 ± 1.0	0.3 ± 0.4	0.63
HDL cholesterol (mmol/l)	1.2 ± 0.1	1.2 ± 0.1	0.02 ± 0.03	1.2 ± 0.1	1.2 ± 0.1	0.004 ± 0.04	0.83
Triglycerides (mmol/l)	1.5 ± 0.2	1.5 ± 0.1	0.04 ± 0.1	1.5 ± 0.2	1.8 ± 0.3	0.3 ± 0.2	0.24
Cortisol (mg/l)	131.7 ± 8.3	131.9 ± 8.8	0.2 ± 7.5	141.8 ± 9.1	145.9 ± 7.8	3.9 ± 7.3	0.72
Epinephrine (μmol/l)	290.9 ± 41.2	251.1 ± 30.6	− 39.8 ± 42.4	227.3 ± 21.3	248.6 ± 28.6	21.2 ± 19.5	0.17
NT-proBNP (pmol/l)	121.1 ± 25.3	118.4 ± 20.5	− 2.6 ± 17.8	122.6 ± 24.6	155.5 ± 27.6	32.9 ± 16.6	0.15
IGF-1 (ng/100 ml)	65.0 ± 4.9	69.3 ± 5.2	4.3 ± 4.9	61.8 ± 5.5	61.5 ± 5.2	− 0.3 ± 2.2	0.39

Values are given as mean ± SE and *P* value is for the comparison of change in intervention group with change in usual care group. hsCRP, high-sensitive C-reactive protein; IGF-1, insulin-like growth factor-1; NT-proBNP, *N*-terminal Pro-B-type natriuretic peptide; TNF, tumor necrosis factor. [a]*P* from *t*-test comparing change between groups.

hospital readmission for heart failure and cardiac death after a mean follow-up of more than 3 years after intervention. The maintenance-training set-up, however, was very costly with hospital-based training thrice a week for the initial 8 weeks and twice a week for an additional 12 months. A study more comparable with the present was the Exercise Rehabilitation Trial study, in which 181 patients (LVEF < 40, 98% NYHA II–III) were randomized to 3 months of supervised training followed by 9 months of home-based training or usual care. One hundred and thirty-nine patients completed the study and no differences were found between the groups in 6MWT ($P = 0.81$) but a trend towards better peak oxygen uptake in the intervention group ($P = 0.08$) was observed [10]. Inconsistent results have been reported from other maintenance programs with unsupervised training, most of them of shorter duration. In a study of 20 older women, improvements in VO_2max and muscle strength achieved during 3 months of supervised training was lost after 3 months of unsupervised training [9]. In a study of 37 patients (LVEF ≤ 35), there was a 26% increase in VO_2max after 16 weeks of hospital-based exercise ($P < 0.001$) but after 8 months of home-based exercise this fell to 8% ($P = 0.07$) [11]. In a study of 175 CHF patients (EF ≤ 40, NYHA II–IV) randomized to home-based walking and resistance training, there were no changes in functional performance or quality of life at 6 months, despite considerable measures to increase adherence, including monthly visit by nurse, providing patients with pedometers and daily and monthly reports by patients on their physical activities [8]. The study hypothesizes that a reason for the lack of effect could be the high proportion of patients receiving β-blocker therapy; 70% in this study versus none of the patients in the study by Belardinelli [8,17]. In this study, 90% of patients received β-blocker therapy, which may contribute to the modest effects.

After adjusting for baseline differences between groups, we did find a significant effect of intervention on the maximum workload. More severe disease as measured by poorer LVEF and lower baseline exercise capacity led to diminished loss of exercise capacity. Although far from cachectic, also patients with BMI less than 30 may have more severe disease, as several studies have shown better survival of CHF patients with high BMI [18]. The smaller decline in these patients may, in part, reflect regression toward the mean but it is also possible that with higher disease severity any exercise program, in this case both intervention and control, may have superior effect because the intervention represents a greater change from the usual level of physical activity. A history of hypertension also led to greater decline in maximum workload perhaps because of a higher degree of diastolic dysfunction in these patients, although this remains speculative.

The discrepancy between effects of intervention as measured by maximum workload and 6MWT or ISWT may relate to the latter tests being less accurate but may also reflect properties of the bicycle ergometer testing. It has been shown that in repeat measurement of maximal exercise capacity this may increase with VO_2max remaining stable, perhaps representing a learning effect [19]. However, as both groups received an initial 8-week exercise training on bicycle ergometer, any learning effect would presumably apply to both. Cardiopulmonary testing with directly measured VO_2max is considered the 'gold standard'

in testing patients with CHF. Unfortunately, cardiorespiratory test facilities were not available at the recruitment hospital, which has patient uptake from a relatively deprived area in Copenhagen. Metaanalyses, however, have shown a homogeneous beneficial effect of exercise training in CHF on maximum workload, exercise duration, and 6MWT [1,20] and self-assessed symptoms and activity show closer correlation to workload than to VO_2max [19]. Thus, the somewhat disappointing results are probably not because of mode of testing.

The change in glucose homeostasis was more beneficial in the maintenance intervention than in the usual care group. Probably because of sedentarism, CHF is associated with insulin resistance [21] and accordingly exercise training has been shown previously to diminish insulin resistance [22] although results are not unequivocal [23]. Furthermore, in this study the metabolic profile also improved by lowering of plasma FFA and glycerol concentrations, which is interpreted as a decrease in overall lipolysis. A marked change in body composition (e.g. a decrease in % adipose tissue) is not a likely explanation. Rather, a decrease in lipolysis is probably because of an increased antilipolytic effect of insulin – in line with the improved insulin action on glucose clearance. Taken together, this set of data shows that although the intensity of the 12 months exercise training was not sufficient to maintain improvements in cardiorespiratory fitness, there was a favorable effect on metabolism (i.e. metabolic fitness). It is well known that low-intensity exercise (e.g. walking) may improve insulin sensitivity, without any measurable effect on cardiorespiratory fitness.

Although plasma FFA and glycerol decreased relatively with exercise training compared with usual care, we found no effect on serum lipids. This was not unexpected, given the high proportion of patients (79%) on statin treatment in this study. Metaanalyses have shown substantial reductions in total cholesterol and triglyceride levels but not in HDL-cholesterol or LDL-cholesterol after exercise-based cardiac rehabilitation of patients with coronary heart disease [24]. Changes in HDL-cholesterol and LDL-cholesterol usually require somewhat higher exercise intensities than those used in this study [25].

Long-term exercise training has an antiinflammatory effect [26], and in this study we found that plasma concentration of high-sensitive C-reactive protein decreased in the intervention but not in the usual care group. In line with some earlier studies on CHF patients [27,28], no effects on plasma concentrations of TNF-α and IL-6 were found. However, a decrease of soluble CD40 ligand and *P*-selectin has been shown despite no significant decrease of TNF-α [28]. Furthermore, plasma concentrations may not necessarily reflect the changes at skeletal muscle level [27]. We found beneficial changes in plasma orosomucoid and urinary excretion of orosomucoid. Urinary orosomucoid has been shown to be associated with inflammation and is also predictive of CHD [29,30]. Further, changes in levels of albumin excretion were in favor of maintenance training. Microalbuminuria, and even very low levels of urinary albumin excretion, reflect endothelial damage and are highly predictive of CHD morbidity [31]. We are not aware of earlier studies showing beneficial effect of exercise training on these parameters.

No significant difference in changes was observed in NT-proBNP, although levels increased in the usual care group and remained stable in the intervention group. Results of earlier studies have been mixed with some but not all studies showing improvements in B-type natriuretic peptide [4,32–34].

This study provides important information on exercise training in a real-life scenario. It is noteworthy that only a small fraction of the initial patients diagnosed with heart failure were in fact eligible for training and less than half of the eligible patients wished to participate. Similar findings were recently reported from a British study in which only 169 of 1639 patients followed in a CHF clinic could be included in a home-based training study [35]. Of the 66 randomized patients, six died during the study and, similar to several other studies [1], dropout rates were high during the next 12 months, despite considerable efforts on the part of the investigators to motivate patients. Even among the 20 completers in the intervention arm, 45% attended less than half of the 26 group training sessions. Unfortunately, the 23 patients who did not complete the study would seem to be the ones that need exercise training the most; they were characterized by more comorbidity and poorer results in initial exercise tests. Thus, the study clearly illustrates the obstacles for successful exercise intervention in real-life clinical settings and confirms findings that patients with low exercise capacity and multiple comorbidities should receive special attention. These findings may question whether the beneficial effects of exercise training reported in the studies of relatively selected patients with CHF could be extended to an everyday clinical setting.

Conclusion

This study illustrates the difficulties in transferring results from trials in selected groups to the clinical reality, where patients are older, have high comorbidity, and low compliance. A low-cost maintenance-training program reduced the decline in the maximum workload compared with usual care but had no effect on other measures of physical function. The maintenance program, however, had a favorable effect on glycemic control, markers of inflammation, and endothelial damage. Further studies that address the problems and benefits

of maintenance training in CHF patients reflecting the demographic characteristics of this patient group are needed.

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Conflicts of interest: none declared.

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Appendix

Fasting venous blood was sampled at baseline, 8 weeks, and 14 months. Serum HbA1c, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, orosomucoid, and creatinine were analyzed right away. HbA1c, glucose, high-sensitive C-reactive protein, orosomucoid, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides were measured by a colorimetric/turbidimetric method (Integra, Roche Diagnostics Scandinavia AB, Glostrup, Denmark). Blood for determination of metabolites and hormones were collected in iced tubes and immediately centrifuged at 4°C. Blood for the determination of tumor necrosis factor α, interleukin 6, high-sensitive C-reactive protein, free fatty acid, and

glycerol was stabilized with EDTA (1.5 mg/ml blood^{-1}). Blood for determination of insulin, insulin-like growth factor 1 (IGF-1) and NT-proBNP was stabilized with 500 Kalikrenin inhibitory units aprotinin (Trasylol) and blood for the determination of epinephrine was stabilized with 5 µm EDTA and 4 µm reduced glutathione in 20 µl of 0.6 N sodium hydroxide (ml blood)$^{-1}$. Until analysis, all plasma samples were stored at −80°C. Insulin was determined with sandwich enzyme-linked immunosorbent assay performed according to the manufacturer's instructions (DakoCytomatics, Glostrup, Denmark). Plasma epinephrine concentrations were determined by a radioimmunoassay kit (Labor Diagnostika Nord, Nordhorn, Germany). Plasma free fatty acid and glycerol analysis was carried out by an enzyme color assay (Hitachi 612, Roche, Glostrup, Denmark). TNF-α and IL-6 were analyzed by flow cell fluorometry (Luminex 100 IS 2.2 system, Luminex, Austin, Texas, USA) by using a commercial kit (LINCO*plex* HSCYTO-60SK KIT, Linco Research, St. Charles, Missouri, USA). IGF-1 was analyzed by ELISA technique (R&D systems Quantikine DG100 assay, Minneapolis, Minnesota, USA). Plasma NT-proBNP analysis was carried out by Electro Chemi Luminescence Technology (Modular, Roche Diagnostics Scandinavia AB, Glostrup, Denmark). Homocystein was measured by fluorescence polarization immune analysis using the Abbot AxSYM System (Abbott Laboratories A/S, Smakkedalen 6, DK-2820 Gentofte, Denmark).