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Original Scientific Paper

The effect of endurance training on exercise capacity following cardiac resynchronization therapy in chronic heart failure patients: a pilot trial

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Background **Both endurance training (ET) and cardiac resynchronization therapy (CRT) improve quality of life (QOL) and exercise tolerance in patients with advanced chronic heart failure (CHF).**

Design **A randomized intervention trial to study the effect on exercise capacity of ET in addition to CRT in patients with CHF and dyssynchrony.**

Methods **Seventeen patients (eight men, aged 59 ± 9 years) with CHF and dyssynchrony were randomized to CRT with ($n=8$) or without ($n=9$) ET and compared with two matched control CHF groups (standard care with ET: $n=9$, standard care only: $n=10$). At baseline and after 5 months, exercise tolerance, left ventricular (LV) remodelling, QOL and NT-pro brain natriuretic peptide (NT-proBNP) levels were assessed.**

Results **Peak oxygen consumption (Vo_2peak), maximal workload (Wattmax), circulatory power, LV ejection fraction, dyssynchrony and QOL improved in both CRT groups. However, the increase in Vo_2peak (+40% versus +16%, $P=0.005$), Wattmax (+43% versus +13%, $P=0.0005$), and circulatory power (+74% versus +32%, $P=0.01$), was significantly greater in the trained versus the untrained CRT patients. Comparison of the four patient groups confirmed the cumulative effects of CRT plus ET.**

Conclusions **ET in resynchronized CHF patients is feasible and further enhances exercise tolerance. Patients with severe CHF should be prescribed an exercise training programme after implantation in order to maximize the expected benefit.** ***Eur J Cardiovasc Prev Rehabil*** **14:99–106 © 2007 The European Society of Cardiology**

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Introduction

Pharmacological therapies that interfere with neurohormonal activation in chronic heart failure (CHF) contribute to fewer heart failure-related hospital admissions and favourably affect survival. However, despite optimal pharmacotherapy, CHF patients are left with functional deficits and reduced physical capacity. To overcome these limitations, rehabilitation programmes, specifically designed for this patient cohort, were introduced as a safe and cost-effective method to increase patients' well-being and exercise tolerance. Six out of the nine randomized controlled trials included in the Extramatch meta-analysis [1] reported a mean increase of 20% in peak oxygen consumption (Vo_2peak) following exercise training [2–7]. This improvement depends not only on baseline patient characteristics, but also on factors such as duration of the programme and training intensity. Although these benefits result mainly from partial

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restoration of endothelial function and skeletal muscle abnormalities, part of the effects may also be attributed to reversed ventricular remodelling [8].

Recent large trials have demonstrated the beneficial effect of cardiac resynchronization therapy (CRT) on prognosis and quality of life in CHF patients with left ventricular dysfunction and left bundle branch block (LBBB) [9,10]. Improved prognosis in these patients was associated with better left ventricular (LV) performance, as evidenced by an increase in LV-ejection fraction, a reduction of LV dimensions and the severity of mitral regurgitation, and changes in V_{O_2}peak ranging from non-significant to a significant increase of 1.8 ml/kg per min [11,12]. Taken together, there is ample evidence that CRT should now be considered in severely symptomatic patients with significant mechanical dyssynchrony. However, to benefit fully from CRT, a multidisciplinary approach combining further pharmacological up-titration with tailored exercise prescription and device optimization is necessary [13].

The present study evaluated the effect on exercise capacity of a 4-month endurance exercise training programme in patients with LV systolic dysfunction and LBBB, referred for CRT. Since both treatment modalities have a different mode of action, we hypothesized that the combination of CRT and physical training would have a cumulative effect. In addition, the impact on quality of life, LV remodelling, LV function and NT-pro brain natriuretic peptide (NT-proBNP) levels were assessed.

Methods

Study population

Seventeen CHF patients, referred for cardiac resynchronization therapy (CRT), were prospectively enrolled and randomized after CRT device implantation to receive either standard pharmacological therapy alone (CRT−; $n = 9$) or to undergo standard pharmacological therapy plus a 4-month-long endurance exercise training programme (CRT+; $n = 8$). Patients were eligible for inclusion if they fulfilled the following criteria: ischaemic or dilated cardiomyopathy, New York Heart Association (NYHA) functional class > III, left ventricular ejection fraction (LVEF) < 35%, left ventricular end-diastolic diameter (LVEDD) > 55 mm, left bundle branch block (LBBB) with QRS duration > 120 ms and in permanent sinus rhythm. All patients were on stable pharmacological treatment for at least 1 month prior to inclusion and had significant inter-ventricular mechanical dyssynchrony (defined by the difference in pulmonary and aortic pre-ejection time intervals > 40 ms measured with Doppler echocardiography). Drug treatment remained unchanged during the study period.

Both randomized resynchronized patient groups were matched to two 'historical' groups of CHF patients who underwent standard pharmacological treatment with (HF+; $n = 9$) or without (HF−; $n = 10$) 4 months endurance exercise training. The latter patient groups were consecutively derived from the database of the cardiac rehabilitation programme (HF+) or the heart failure clinic (HF−) if they fulfilled the following criteria: ischaemic or dilated cardiomyopathy, NYHA > III, LVEF ≤ 35%, LBBB with QRS > 120 ms.

The study was approved by the institutions' local ethical committees and all patients gave their written informed consent.

Study protocol

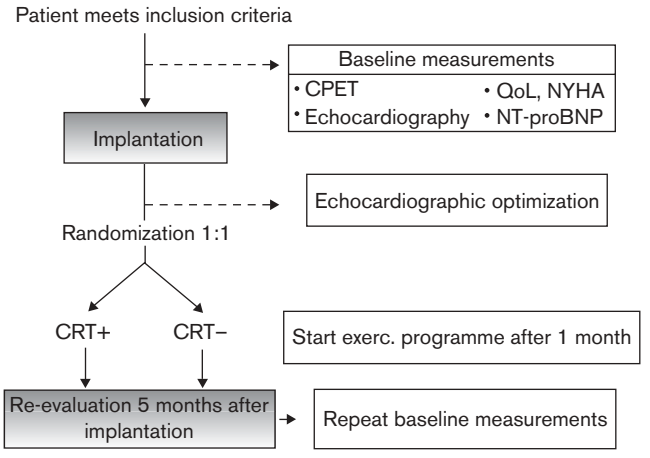
The design of the study is summarized in Fig. 1. Following CRT implantation, patients were randomized to attend either an exercise training programme (CRT+) or to undergo standard therapy (CRT−) only. In order to recover from the procedure and to prevent lead dislocation, patients were allowed 1 month of relative rest before starting the exercise programme.

All data, including clinical and echocardiographic evaluation, cardiopulmonary exercise testing (CPET) with gas analysis, NT-proBNP sampling and the Minnesota Living With Heart Failure Questionnaire were collected prior to CRT implant (baseline) and at the end of the study.

Cardiac resynchronization therapy device implantation

In 15 patients, left ventricular leads were implanted transvenously (Easytrak lead; Guidant Corp., St Paul, Minnesota, USA) and placed in the basal mid posterolateral vein. In two patients, the left ventricular lead was

Fig. 1



Study protocol. CRT, cardiac resynchronization therapy; CRT+, pharmacological therapy plus exercise training programme; CRT−, pharmacological therapy only; CPET, cardiopulmonary exercise testing; QoL, quality of life; NYHA, New York Heart Association; NT-pro brain natriuretic peptide (NT-proBNP).

inserted on the LV epicardium through a robot-assisted thoracoscopic approach. All leads were connected to a CRT pacemaker (Contak TR, Guidant Corp.; $n = 13$) or an implantable cardioverter defibrillator (Contak CD, Guidant Corp.; $n = 4$). The pacemaker was programmed in DDD mode and device settings were optimized using echocardiography, as described previously (mean atrioventricular delay = 104 ± 5 ms) [14]. No lead dislocation occurred at follow-up and all LV thresholds remained within normal limits.

Training protocol

Patients attended a supervised ambulatory exercise programme consisting of 3 sessions/week, each lasting for 1 h. Each session started with a 5 min warming-up and stretching period, followed by endurance training (cycling, walking) and a period of 5 min cooling-down. The target heart rate during exercise was defined as the heart rate achieved at 90% of the ventilatory threshold during CPET.

Data analysis

Cardiopulmonary exercise testing with gas analysis

Every patient performed a symptom-limited exercise test on a computer-driven cyclo-ergometer at baseline, after 1 month, after 3 months and at the end of the study period (5 months). Interim CPETs were used to adjust training intensity. To obtain an optimal duration of the CPET between 8 and 10 min, two ramp protocols were used; patients started either with 20 or 40 Watts, with an incremental load of 10 versus 20 Watts every minute, respectively. Twelve-lead ECG and heart rate were recorded continuously, whereas automatic cuff blood pressure was measured every 2 min and at peak exercise. Exercise tests were supervised by an expert team consisting of physiotherapists and physicians who were unaware of previous CPET results or of the patient's participation in the training programme. Online analysis of VE/V_{O_2} and VE/V_{CO_2} curves allowed us to encourage patients to exercise up to exhaustion.

Breath-by-breath gas exchange measurements were performed using a metabolic cart. Ventilation (VE), oxygen uptake (V_{O_2}) and carbon dioxide production (V_{CO_2}) were determined on-line every 15 s. Peak oxygen consumption (V_{O_2}peak) was expressed as the highest attained V_{O_2} during the final 30 s of exercise. The anaerobic threshold (AT) was defined by the V-slope method. The slope of the relation between VE and V_{CO_2} was calculated by linear regression, excluding the non-linear part after reaching the ventilatory threshold. Circulatory power was calculated as V_{O_2}peak × systolic blood pressure at peak exercise [15].

Echocardiography

Echocardiography was performed according to the guidelines of the American Society for Echocardiography [16]. Resting M-mode echocardiographic measurement of left ventricular end-diastolic (LVEDD) and end-systolic diameter (LVESD) was performed from the parasternal long axis. Left ventricular ejection fraction was quantified according to the modified Simpson's rule [17]. The interventricular mechanical delay was determined by using conventional pulsed-wave Doppler and defined as the difference in pulmonary and aortic pre-ejection time intervals. Echocardiographers were blinded to the study intervention.

NT-proBNP measurement

Fasting blood samples were collected between 0800 and 0900 h, at baseline and at the end of the study period. Care was taken to avoid blood sampling within 24 h following exercise training or CPET. EDTA-plasma was separated by centrifugation and stored at −20°C. NT-proBNP was determined with a sandwich immunoassay on an Elecsys 2010 (Roche Diagnostics GmbH, Mannheim, Germany). The analytical range of this assay extends from 5 to 35 000 pg/ml. The coefficient of variation was 1.3% ($n = 10$) at a level of 221 pg/ml and 1.2% ($n = 10$) at a level of 4091 pg/ml.

Statistics

All data are expressed as mean value ± SEM. Numerical/binary data were analysed using the chi-squared test. For continuous variables, inter-group comparisons were made using the Mann–Whitney test. Differences between groups (trained versus control) and changes over time within each group (time effect), as well as any interaction (different trends over time between groups) were assessed by two-way repeated measures analysis of variance (ANOVA). Correlations were determined with the Spearman's correlation test. A P value < 0.05 was considered statistically significant. All statistical analyses were performed using the software package SPSS, version 11.0.3 (SPSS Inc., Chicago, Illinois, USA).

Results

Patient characteristics

Baseline characteristics were similar in CRT + and CRT − patients and did not differ from the control groups of CHF patients (HF + and HF − groups) (Table 1). All patients were on standard medical treatment, without an inter-group difference ($P > 0.5$). Drug treatment remained unchanged during the study period.

Functional and echocardiographic effects of endurance training in cardiac resynchronization therapy-treated patients

Both CRT-treated groups showed a significant improvement in V_{O_2}max, Wattmax and circulatory power (Table 2). The observed effect, however, was significantly greater in the CRT + versus the CRT − group. Of note, V_{O_2}max increased by 40% (13.8 ± 1.0 ml/kg per min before, 19.3 ± 1.2 ml/kg per min after training) in the CRT + group, whereas the increase in the CRT − group was

Table 1 Demographic characteristics

	Randomized CRT groups		Control groups			
	CRT+	CRT−	CRT+ versus CRT−	HF+	HF−	Comparison 4 groups
	(*n*=8)	(*n*=9)	*P*	(*n*=9)	(*n*=10)	*P*
Age (years)	57±2	61±4	0.2	65±3	64±4	0.3
Male/female	3/5	5/4	0.6	7/2	7/3	0.3
CAD/IDCM	1/7	3/6	0.6	6/3	7/3	0.05
V_{O_2}max (ml/kg per min)	13.8±1.0	11.9±0.9	0.2	12.1±1.1	13.2±0.5	0.5
Wattmax	79±11	77±7	0.7	79±5	83±8	0.9
NYHA	3.1±01	3.0±0.0	0.7	3.0±0.0	3.0±0.0	0.3
MLHF	51±9	36±8	0.2	NA	NA	–
LVEDD (mm)	68±2	74±3	0.3	70±2	71±3	0.6
LVESD (mm)	58±2	62±4	0.5	58±2	57±2	0.9
LVEF (%)	27±5	28±5	1.0	28±3	26±2	0.8
QRS width (ms)	169±9	187±9	0.2	161±8	167±9	0.1
IV delay (ms)	66±7	78±5	0.1	NA	NA	–
NT-proBNP (pg/ml)	2325±785	1269±296	0.3	NA	NA	–
Treatment						
ACE inhibitor or ARB	8 (100%)	9 (100%)	1.0	7 (78%)	10 (100%)	0.1
Diuretics	7 (88%)	8 (89%)	1.0	7 (78%)	9 (90%)	0.9
Beta-blockers	8 (100%)	9 (100%)	1.0	8 (89%)	7 (70%)	0.1
Digoxin	1 (13%)	5 (56%)	0.1	2 (22%)	3 (30%)	0.2
Spironolactone	7 (88%)	8 (89%)	1.0	7 (78%)	6 (60%)	0.4

CRT, cardiac resynchronization therapy; CRT+, pharmacological therapy plus exercise training programme; CRT−, pharmacological therapy only; HF+, CHF patients who underwent standard pharmacological treatment with endurance exercise training; HF−, CHF patients who underwent standard pharmacological treatment without endurance exercise training. CAD, coronary artery disease; IDCM, idiopathic dilated cardiomyopathy; NYHA, New York Heart Association; MLHF, Minnesota Living with Heart Failure Questionnaire; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; IV, interventricular; NT-proBNP, NT-pro brain natriuretic peptide; NA, not available; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

limited to 16% (11.9 ± 0.9 ml/kg per min before, 13.8 ± 0.9 ml/kg per min after 5 months; $P = 0.005$ for interaction). The gain in maximal workload (CRT+ versus CRT−: +43% versus +13%, $P = 0.0005$ for interaction) showed a comparable evolution. The observed difference for circulatory power was also in favour of the trained CRT group ($P = 0.01$ for interaction, Table 2). The CRT+ group had a significantly greater improvement in sub-maximal exercise capacity (as evidenced by the higher V_{O_2} and workload at AT) as compared to the CRT− group ($P = 0.006$ and 0.001 for interaction, respectively). Changes in O_2 pulse at peak exercise and VE/V_{CO_2} slope were not different according to treatment modality.

In order to unravel the contribution of cardiac rehabilitation upon the beneficial effects of CRT, V_{O_2}max of the trained versus the un-trained CRT group were compared to each other at four time points (i.e. baseline, after 1 month, after 3 months, end of the study = 5 months). Figure 2 illustrates the evolution of V_{O_2}max in both the CRT+ and the CRT− patients. After 1 month (before the start of the training programme in CRT+ group), V_{O_2}max was similar in both groups (14.1 ± 1.3 ml/kg per min for the CRT+ group versus 14.4 ± 0.9 ml/kg per min for the CRT− group, $P = 0.7$). Thereafter, however, V_{O_2}max remained unchanged in the CRT− group, whereas it increased gradually during the rehabilitation programme in the CRT+ patients ($P = 0.003$).

The higher V_{O_2}max at the end of the study in the CRT+ as compared to the CRT− group was not related to a greater reduction in electrical or mechanical dyssynchrony (Table 2). Moreover, both CRT groups also benefited equally in terms of left ventricular remodelling; LVEDD and LVESD diameters were reduced, whereas LVEF was significantly increased (Table 2).

Despite greater benefit in exercise capacity in the CRT+ versus the CRT− group, NYHA functional class and QOL (Minnesota Living with Heart Failure Questionnaire) evolved similarly (Table 2). The inter-group difference for NT-proBNP was not significant.

Cumulative effect of cardiac resynchronization therapy and endurance training

Figure 3 compares the evolution of V_{O_2}peak (Fig. 3a), Wattmax (Fig. 3b) and circulatory power (Fig. 3c) in the CRT+ and the CRT− groups, together with changes observed after a similar time interval in patients who received standard medical therapy (HF−) or standard therapy and exercise training (HF+). At follow-up, no significant improvement in V_{O_2}peak, maximal workload or circulatory power was noted in the HF− group, whereas HF+ and CRT− patients demonstrated a similar net increase in V_{O_2}peak. Interestingly, those patients who underwent CRT followed by the endurance training programme (CRT+) not only had significantly better exercise capacity compared to the other groups, but the beneficial effects appeared to be potentiated by each treatment modality.

Discussion

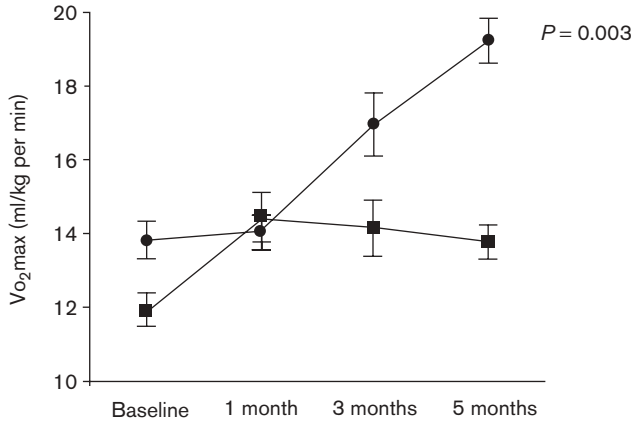
The present study is the first to examine the effects of endurance training in patients with severe chronic heart

Table 2 Effects of exercise training after CRT (CRT+) versus CRT only (CRT−)

	CRT+ ($n=8$)			CRT− ($n=9$)			
	Baseline	5 months	*P* intra-group	Baseline	5 months	*P* intra-group	*P* (ANOVA)
V_{O_2}peak (ml/kg per min)	13.8±1.0	19.3±1.2	0.01	11.9±0.9	13.8±0.9	0.02	0.005
Watt peak	79±11	113±12	0.01	77±7	87±9	0.04	0.0005
Circulatory power*	1558±84	2714±148	0.01	1581±197	2093±312	0.02	0.01
V_{O_2} AT (ml/kg per min)	9.1±0.5	12.5±1.0	0.02	9.0±0.9	8.3±0.6	0.4	0.006
Watt AT	44±3	64±7	0.03	69±11	49±7	0.02	0.001
VE/V_{CO_2} slope	32.0±2.1	29.4±1.2	0.4	34.4±1.6	29.0±1.8	0.05	0.4
O_2 pulse peak (ml O_2/beat)	9.8±0.8	12.9±1.4	0.02	9.0±0.7	11.0±1.1	0.02	0.6
HR rest	79±6	74±4	0.2	75±4	67±3	0.6	0.6
HR peak	120±5	129±3	0.09	118±5	112±7	0.05	0.1
SAP peak (mmHg)	116±8	141±4	0.02	131±11	148±16	0.07	0.6
NYHA	3.1±0.1	2.1±0.3	0.04	3.0±0.0	2.1±0.3	0.02	0.8
MLHFQ	51±9	30±6	0.05	36±8	24±7	0.1	0.5
LVEDD (mm)	68±2	59±3	0.01	74±3	68±4	0.06	0.3
LVESD (mm)	58±2	47±3	0.01	62±4	54±5	0.02	0.3
LVEF (%)	27±5	36±5	0.02	28±5	34±6	<0.05	0.5
QRS width (ms)	169±9	146±10	0.03	187±9	162±9	0.008	0.8
IV delay (ms)	66±7	19±7	0.02	78±5	30±9	0.008	0.9
NT-proBNP (pg/ml)	2325±785	1698±802	0.1	1269±296	711±198	0.01	0.7

AT, anaerobic threshold; HR, heart rate; SAP, systolic arterial pressure; NYHA, New York Heart Association; MLHF, Minnesota Living with Heart Failure Questionnaire; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; IV, interventricular; NT-proBNP, NT-pro brain natriuretic peptide. *Circulatory power in mmHg/ml V_{O_2} per kg per min^2.

Fig. 2



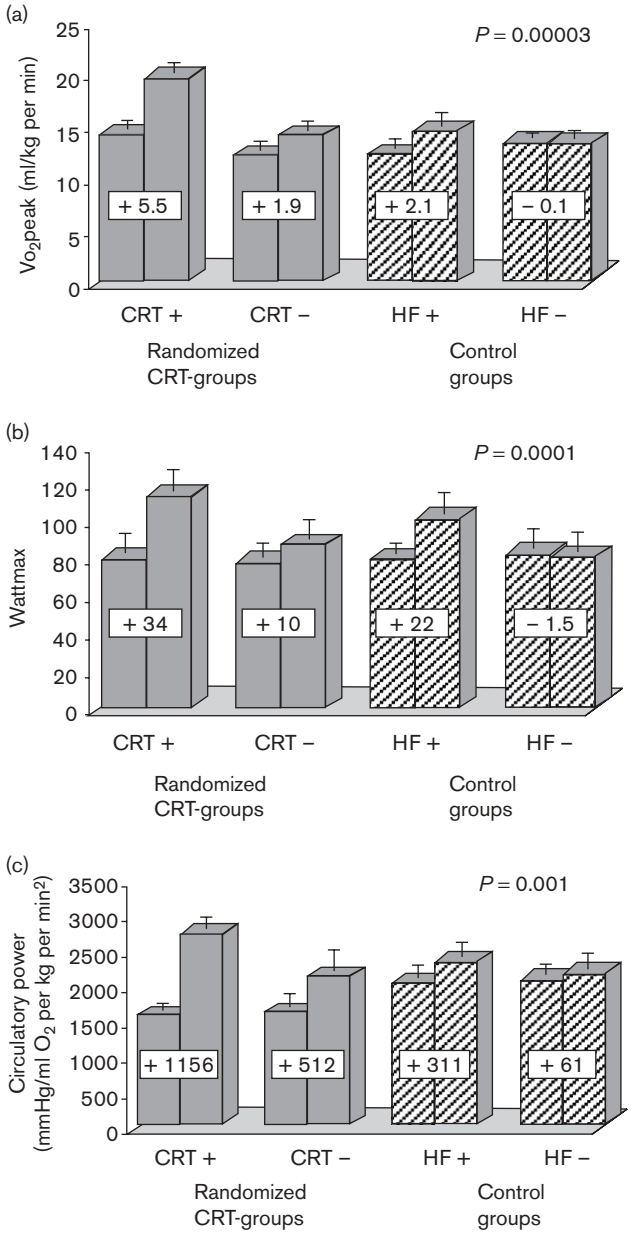
Evolution of V_{O_2}max for the CRT+ (pharmacological therapy plus exercise training programme; ●) and CRT− (pharmacological therapy only; ■) groups.

failure (CHF) following cardiac resynchronization therapy (CRT). Four months of endurance training in these patients provided a distinct cumulative benefit in terms of exercise capacity measured through objective parameters, such as peak oxygen consumption (V_{O_2}peak), maximal workload (Wattmax) and circulatory power. The marked improvement in exercise performance in CRT+ versus CRT− patients was not paralleled by more pronounced reverse left ventricular (LV) remodelling. This finding suggests indirectly that in this target population physical rehabilitation-related benefits were not due to central effects but more likely the result of peripheral adaptations.

Triple therapy (angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, beta-blockers, spironolactone) for NYHA class III or IV CHF patients reduces mortality significantly and is considered standard treatment [18]. Recent efforts to further interrupt the up-regulated humoral systems have not been successful, suggesting that the ceiling for neurohormonal blockade might have been reached [19,20]. An easily overlooked problem with medical therapy in this particular population is that achievements in terms of hard endpoints are not always paralleled by enhanced exercise capacity. In fact, critical appraisal of the literature with regard to the effect of angiotensin-converting enzyme inhibitors and beta-blockade in CHF provides equivocal results. Most studies and meta-analyses are flawed due to the fact that functional capacity is usually assessed using a 6-min walk test or crude determination of exercise duration without formal CPET. Although a recent meta-analysis of ACE-inhibitor trials showed an increase in exercise duration of 30 s, no difference in V_{O_2}peak was reported using objective CPET [21]. Exactly the same caveats apply to beta-blocker studies, of which only four out of 20 randomized placebo-controlled trials assessed V_{O_2}peak with a neutral result [22].

The perception of pharmacological limitation and the advent of CRT have supported the notion that a more mechanistic approach might be valuable. Through primary electrical and consequently mechanical resynchronization, CRT achieves one of the major surrogate endpoints of neurohormonal antagonists – reverse left ventricular remodelling. The reduction of ventricular dimensions and mitral regurgitation, and the increase in left ventricular ejection fraction without additional

Fig. 3



Comparison of (a) changes in peak oxygen consumption (Vo_2peak); (b) changes in maximal workload (Wattmax) and (c) changes in circulatory power in groups given pharmacological therapy plus exercise training programme (CRT+); pharmacological therapy only (CRT–); and in chronic heart failure patients who underwent standard pharmacological treatment with (HF+) and without (HF–) endurance exercise training. *P*=level of significance between the four groups.

myocardial oxygen demand, enhance effective cardiac output [23]. By halting the process of ventricular remodelling on the one hand, and by increasing cardiac performance on the other hand, CHF patients benefit from both lower mortality, higher quality of life and reduced heart failure-related hospitalizations [9,10]. Exercise capacity and the ability to perform daily life tasks are major determinants of quality of life. Most clinical CRT trials have assessed this issue using semi-quantitative methods such as the 6-min walking test. In the few randomized CRT trials that included formal exercise testing with gas analyses, the observed increase in Vo_2peak was small to moderate [11,12].

Physical rehabilitation of CHF patients has been practised on a small scale for many years. Universal acceptance of this treatment modality in this particular patient group, however, has awaited larger outcome trials, providing hard endpoints on morbidity and mortality. The Extramatch meta-analysis compiled data from nine randomized endurance training programmes, in which 801 patients were enrolled [1]. In their paper, Piepoli *et al*. [1] show that tailored exercise prescription significantly reduced mortality by 35% after 2 years' follow-up. Looking at six of the trials for which CPET data are available, 2–12 months training improved Vo_2peak from 17.2 to 20.6 ml/kg per min [2–7]. In the ELVD trial [8], 6 months of endurance training significantly improved left ventricular remodelling and increased left ventricular ejection fraction. These reassuring data not withstanding, it is believed that the effects of comprehensive training protocols are diverse and to a large extent relate to the partial correction of peripheral abnormalities. It has been documented extensively that exercise training improves endothelial dysfunction and reduces peripheral resistance through the up-regulation of endothelial nitric oxide synthase (eNOS) [24], the abrogation of both oxidative stress [25] and the low-grade inflammatory status [26,27] characteristic of moderate to severe CHF and by down-regulating the activated neuro-endocrine axis [28,29]. Moreover, skeletal muscle atrophy and strength are addressed, with a re-shift from type II to type I muscle fibres and the up-regulation of local growth factors [i.e. insulin-like growth factor-1 (IGF-1)] [30]. Despite the limitation of a small patient group, the present study supports the hypothesis that a cumulative benefit can be derived from the combination of two interventions that focus on different aspects of the heart failure syndrome. In the combined CRT+ training group, Vo_2peak increased by 5.5 ml/kg per min, representing a relative benefit of 40%. The absolute increase in Vo_2peak of 1.9 ml/kg per min observed in the CRT– group not participating in the exercise programme is in agreement with the current literature. In order to discern the specific contribution of endurance training in the CRT+ group, data from a case-matched patient group with comparable disease severity and electrical dyssynchrony were included. In the latter HF+ group, Vo_2peak changed from 12.1 ml/kg per min at baseline to 14.2 ml/kg per min after the training period. Although this gain in aerobic capacity is somewhat less than expected from the compiled data in the Extramatch study [1], it compares favourably with the results of the ELVD trial [8], in which a total of 90 CHF patients with more advanced

disease were randomized to a 6-month endurance training programme or to a control group. In this landmark trial, patients with a markedly reduced left ventricular ejection fraction (i.e. mean LVEF of 25 ± 4%) improved their baseline Vo_2peak of 13.8 ± 2.3 ml/kg per min by 2.4 ml/kg per min. The superior effect on exercise capacity of the combined CRT + training regimen is also reflected in a 43% relative increase in maximal workload. Circulatory power, a recently validated independent prognostic variable [15], also increased more in the CRT + group compared to the CRT – patients. This non-invasive surrogate of cardiac power might be of particular relevance in the current setting, because it combines both central cardiac performance with peripheral indices at peak exercise.

Whereas objective assessment of exercise capacity clearly showed a superior effect in the CRT + group, the lack of a more pronounced amelioration in both NYHA class and Minnesota Living with Heart Failure Questionnaire (MLHFQ) in the CRT + group is surprising. It should be stressed, however, that the implantation of a device might have an important placebo effect. Of note, in the MIRACLE study [31], 6 months after the implantation of the bi-ventricular pacemaker, the MLHFQ score decreased by 9 points in the control group (non-paced) whereas Vo_2peak remained nearly unchanged (+ 0.2 ml/kg per min). Our findings agree with the MIRACLE data: there was a similar reduction of 12 points in the CRT – group, which was smaller although not significantly different from the 21 point reduction in the CRT + group. We suspect that the absence of a statistically significant difference between both groups may be explained partly by the small number of patients included.

Since endurance training has been shown to modulate neurohormonal activation [28,29], a more distinct decrease in NT-proBNP levels could have been anticipated in the CRT + patients. Again, the fact of including small patient groups and, in addition, the relatively short follow-up time might be responsible for the lack of a difference in NT-proBNP levels between CRT – and CRT + patients at follow-up.

The fact that parameters affecting resynchronization (i.e. QRS width and inter-ventricular mechanical delay) and left ventricular remodelling evolved similarly in both CRT groups is reassuring. These findings suggest that the observed improved exercise capacity in the CRT + versus the CRT – patients is not the consequence of more optimal resynchronization, which could have led to a higher number of 'responders' in the former group.

The number of patients enrolled in this pilot trial was small. However, through the specific design of a multi-centre randomized trial, we aimed at minimizing the chances of selection bias.

At first glance, the results of this study indicate the expected benefit of a rehabilitation programme in CHF patients. However, an improvement of 40% in Vo_2peak has not been shown previously in a patient group with comparable disease severity. Moreover, data from the literature on the effect of both exercise training and CRT on the one hand, and the changes in Vo_2peak observed in the control groups on the other hand, argue against this assertion. We therefore believe that the present findings point in the direction of a cumulative benefit of the combination of CRT with training.

In conclusion, despite multi-faceted medical treatment, CHF patients are left with functional deficits and impaired quality of life. The recent introduction of CRT has revolutionized the approach to patients with severe CHF, offering both improved prognosis and less morbidity. The present small pilot trial suggests that exercise training after CRT is safe and provides a cumulative benefit in terms of exercise capacity, which is a major goal in severely debilitated patients. Larger prospective studies are needed to further elaborate the role of cardiac rehabilitation in this patient cohort.

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