European Heart Journal (1998) **19,** 466–475

Experience from controlled trials of physical training in chronic heart failure

Protocol and patient factors in effectiveness in the improvement in exercise tolerance

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Background Beneficial effects of physical training on exercise tolerance, autonomic and skeletal muscle function and limb blood flow have been demonstrated in chronic heart failure. Because this rehabilitation is expensive, may involve risk, and has unknown effects on prognosis, the possibility of predicting benefit on the basis of individual patient data is intriguing. The most suitable exercise training programme has not yet been established.

Methods and Results We reviewed the progress of 134 stable heart failure patients studied in randomized controlled trials of physical training. A significant training effect (+13% peak oxygen consumption, +17% exercise duration) was associated with improved autonomic indices (resting catecholamines and hormones, heart rate variability), without significant side-effects. No ventilatory, haemodynamic, autonomic or clinical factor at baseline was a predictor of outcome. Similar beneficial effects were observed in both male and female patients. The improvement in oxygen consumption after 16 weeks training was higher than after 6 weeks ($+2{\cdot}6 \pm 3{\cdot}0$ vs $+0{\cdot}3 \pm 3{\cdot}1$ ml . kg . min^{-1}, $P<0{\cdot}05$). The combination of cycle ergometer with calisthenic exercises was more beneficial than cycle ergometer alone ($+2{\cdot}7 \pm 4{\cdot}2$ vs $1{\cdot}2 \pm 2{\cdot}0$ ml . kg . min^{-1}, $P<0{\cdot}01$). The presence of non-sustained ventricular tachycardia did not preclude a training effect. Patients older than 70 years were able to train, although less effectively than the younger ones. No difference in exercise gain was observed whether the patients trained in the hospital or at home.

Conclusion The positive effects of physical rehabilitation in chronic stable heart failure patients are confirmed. No baseline patient factor was significantly correlated with outcome. A tailored, moderate, home-based, combined cycle ergometer, plus calisthenic exercise training seems safe and beneficial in a large cohort of heart failure patients, with similar benefits in a variety of conditions and different hospital settings.
(Eur Heart J 1998; 19: 466–475)

Key Words: Autonomic control, exercise, heart failure, haemodynamics, rehabilitation, ventilation.

Introduction

Chronic heart failure is a major health problem with a large socio-economic burden of chronic disease, handicap and dependency. Its overall incidence in the general population is between 0·5–1·5% with a 4-year mortality of 35%[1]. It is a multisystem syndrome with a variety of pathophysiological abnormalities which reduce exercise tolerance and contribute to the symptoms of functional disability[2]. The patients are likely to benefit substantially from even modest improvements in their ability to perform exercise as many daily tasks will stress them close to the limits of their cardio-pulmonary exercise reserve.

A number of groups have now shown that patients with severe left ventricular dysfunction can be safely entered into exercise training programmes and that by the usual indices of exercise heart rate, ventilatory and peak oxygen consumption (peak$\dot{V}O_2$) responses achieve a favourable training response[3]. Sullivan *et al.*[4] demonstrated that 4–6 months of aerobic training increased exercise capacity and both blood flow and oxygen extraction in the exercising limb. Studies from our group confirmed the benefit of exercise training in chronic heart failure using, for the first time, a randomized controlled design, and a home exercise regimen[5–8].

Revision submitted 4 July 1997, and accepted 10 July 1997.

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0195-668X/98/030466+10 $18.00/0 hj970736

The growing literature on exercise and muscle physiology in chronic heart failure supplies some answers[9–11] as well as raising a number of important questions. The identification of patients who might benefit most from an exercise programme or be at risk of harm would have important clinical implications, particularly in relation to disability and reimbursement. Because cardiac rehabilitation can be expensive, and could involve a certain risk, the idea that effort, expenditure and risk could be avoided if a low likelihood of benefit was predicted on the basis of initial patient data is crucial. Although previous findings provide some baseline data[5,12–24] only larger studies could determine whether any factor may predict success or failure of exercise training.

The European Heart Failure Training Group is a collaboration between European teams of researchers and clinicians interested in the rehabilitation of patients with cardiovascular disabilities. The Group brings accumulated experience in a research network to assess the benefit of an exercise physical training programme as secondary prevention in chronic heart failure.

We performed an overview of randomized controlled trials of exercise training in chronic heart failure patients performed by our group to identify (1) the patients most likely to benefit from physical training, (2) the clinical factors which may be related to a poor response to exercise training, (3) the most beneficial exercise training protocol for this high risk group of patients.

Methods

The study collaborators comprised units which had worked together on physical training projects in chronic heart failure with Professor Andrew Coats either in Oxford or London.

All studies were approved by local ethics committees and all subjects gave written informed consent. After initial full clinical assessment, which included cardiopulmonary exercise testing, the subjects were randomized into controlled comparisons of training versus detraining. During detraining, patients were requested not to take part in any exercise programme. Two to three baseline laboratory visits were used to familiarize the patients to the exercise tests and other laboratory procedures. The physicians conducting the tests were unaware of the training status of the subjects.

Patients

The entry criteria in all the centres were similar: stable New York Heart Association functional classification (NYHA) class I–III, chronic heart failure of at least 3 months' duration, with no changes in medication, stable sinus rhythm, limitation of exercise by breathlessness or fatigue on exercise. No patient was limited by angina or claudication or had peripheral oedema at the time of the study. At baseline, radionuclide ventriculography was performed to assess left ventricular ejection fraction; the presence of non-sustained ventricular tachycardia was evaluated on 24 h ECG Holter monitoring.

Table 1 Patient characteristics (n = 134)

Age (years)	60·5 ± 8·6 (range 44–77)
Ejection fraction (%)	25·0 ± 8·9 (range 9–43)
Sex	Male-126 (94%); Female-8 (6%)
NYHA class	I-3 (1·5%); II-67 (50·0%); III-64 (48·4%)
Aetiology	IHD-104 (77·7%); DCM-30 (22·2%)
Therapy	
ACE-inhibitors	78·5%
Diuretics	92·9%
Digoxin	31·7%
Amiodarone	15·7%
Nitrate	14·2%

Mean ± SD (%); NYHA class, New York Heart Association classification; IHD = ischaemic heart disease; DCM = dilated cardiomyopathy.

Table 1 presents the characteristics of the study population: 134 patients initially entered the trials, the majority were male, with mild to moderate chronic heart failure (NYHA class II–III).

Training programme

All patients trained on a cycle ergometer for 20 min 4–5 days/week. The patients were instructed to 'warm-up' each day at 25 W for 1–3 min and then to increase the resistance setting until the heart rate was 70–80% of the predetermined peak heart rate. After 20 min exercise the patients would 'cool down' for 1–3 min at 25 W. The actual mean heart rate reached during cycle ergometer exercise training was $133{\cdot}1 \pm 25{\cdot}6$ beats . min^{-1}. In 75 patients (55·9%) the compliance was assessed by means of the number of bicycle wheel revolutions achieved at the end of the training period and expressed as a percentage of the sum of the number expected.

Fifty-four patients (40·3%) also performed calisthenic exercise with stationary running 5 days/week. The calisthenic exercises were prescribed according to the recommendations of Canadian Air Force XBX for Women Programme: the exercises 1 to 10 of chart 1 were prescribed to be performed gradually in a total time of 12 min. Patients were asked to keep a daily calendar.

The duration of the training ranged from 6 weeks (8·9% of the patients), 8 weeks (48·5%), 10 weeks (11·9%), 12 weeks (11·2%), to 16 weeks (19·4%). The majority of the patients (69·4%) trained at home, 19·4% trained only in hospital, and 11·2% trained partially in hospital and partially at home.

Clinical assessment

Full clinical assessment was performed after training and after detraining and included baseline heart rate, blood pressure and symptom evaluation (NYHA class).

Exercise protocols and cardiopulmonary assessment

All patients underwent symptom-limited exercise testing on their first assessment, after detraining and after training. In 121 patients (90·3%) a symptom-limited cycle exercise test using increments of 25 W every 5 min was used. In 13 patients (9·7%) a standard Bruce treadmill protocol was used with the addition of a stage '0' consisting of 3 min at 1 mile per hour with a 5% gradient. Patients exhaled through a one-way valve connected to a system to determine respiratory gas exchange data continuously throughout the exercise test. The gas meters were calibrated prior to each run against a known gas concentration. Patients were encouraged to exercise to exhaustion. Peak $\dot{V}O_2$ (ml . kg . min^{-1}) and exercise duration until exhaustion (min) were calculated. The ventilation/carbon dioxide production slope ($\dot{V}E/\dot{V}CO_2$) was used as an index of the ventilatory response to exercise. At peak exercise the chronotropic response (i.e. the exercise induced increased in heart rate) and the blood pressure were computed. In the patients who performed cycle ergometer exercise test, exercise load performed (maximal watts) was computed.

Autonomic nervous system measures

Measurements of venous noradrenaline were made at rest and at peak exercise in 43 patients. In 11 patients, resting measurements of plasma renin activity, aldosterone, atrial natriuretic peptide and adrenaline were performed at rest, at the same time of day, by methods described elsewhere[25–27]. Plasma and serum were stored at −80 °C until assayed. Plasma renin activity, aldosterone and atrial natriuretic peptide were measured by radioimmunoassay with standard kits, while catecholamines were measured by high performance liquid chromatography with electromechanical detection.

In 57 patients, heart rate variability was computed as a measure of the autonomic nervous system. Resting recordings of 640 consecutive heart beats were made in a quiet darkened room on a Store 4 Racal-Thermispeed FM tape recorder (Southampton, U.K.) with the patients in the supine position. These recordings were analysed by autoregressive power spectral analysis of heart rate variability. Standard deviation, high (0·18 to 0·40 Hz) and low (0·03–0·15 Hz) frequency components were calculated as previously described[5,28]. The high frequency fluctuations are coincident with respiratory sinus arrhythmia and reflect vagal tone, while the low frequency components are influenced by both vagal and sympathetic activation.

Statistical analysis

The trials were analysed according to the recommendations of Hills and Armitage for crossover trials[29] and analysed for the presence of period or carry-over effects, none of which was found. Analysis of variance was used to compare data after training with data after detraining, followed by Student's t-test for normally distributed parameters, and the Wilcoxon signed rank test for non-normally distributed parameters. Simple and multiple linear correlations between variables were derived by the least square method to determine the relationship between the investigated variables. Significance lower than the 5% level was taken to be significant, and corrected where appropriate for multiple comparison testing by the Scheffe procedure. The patients were identified as 'responders' to physical training if they showed a >10% increase in peak $\dot{V}O_2$[12]. Data are expressed as absolute and percentage means (± mean standard deviations).

Results

No complications were reported relating to the training protocol or to any of the investigations performed. Eight patients did not complete the programme. No significant differences in clinical characteristics were observed between drop-outs and trained patients. All drop-outs occurred in the control phase: in five, death followed progressive worsening of heart failure, three underwent cardiac transplantation after admission with severe cardiac failure. The remaining 126 patients completed the trials without adverse events and with no change in drug therapy. The compliance to the cycle ergometer training programme, as assessed in 75 patients, was good with a mean (range) compliance of 85 ± 12% (74–101%). Compliance with the calisthenic exercises was 92·1 ± 9%. Tables 2 and 3 summarize the effects of physical training.

General training results

No adverse training-related side effects were reported by the subjects. A general improvement in symptoms of breathlessness was evident, as illustrated by the significant reduction in NYHA class (−0·45, $P<0·0001$) (Table 2).

Exercise testing and cardiopulmonary measurements

No significant changes were observed after detraining with respect to baseline. Training increased peak $\dot{V}O_2$ compared to detraining (+1·8 ± 3·2 ml . kg . min^{-1}, +13·0 ± 21·6%, $P<0·01$), and the VE/VCO_2 slope was reduced (−3·2 ± 4·5, −8·0 ± 9·7%, $P<0·01$) (Table 2). Peak exercise duration was prolonged by +1·7 ± 1·8 min (+17·7 ± 21·5%, $P<0·001$) (Table 2), with a higher workload (from 77·3 ± 27·6 W to 90·6 ± 29·3 W, +22·1 ± 35·2%, $P<0·0001$). Resting heart rate was

Table 2 Effect of physical training on exercise testing and ventilatory function

Variable	Detraining	Training
NYHA class	2·48 ± 0·54	2·03 ± 0·53***
Peak $\dot{V}O_2$ (ml . kg . min^{-1})	15·46 ± 4·94	17·32 ± 6·04*
Exercise duration (min)	11·62 ± 4·20	13·40 ± 4·62**
$\dot{V}E/\dot{V}CO_2$	35·96 ± 8·56	32·75 ± 6·82*
Heart rate at rest (beats . min^{-1})	81·77 ± 14·26	79·21 ± 12·46
Chronotropic response (beats . min^{-1})	50·82 ± 21·93	64·17 ± 22·31***
Systolic blood pressure		
at rest (mmHg)	118·57 ± 18·08	118·25 ± 18·09
at peak exercise (mmHg)	151·77 ± 28·90	164·60 ± 37·87*

Mean ± SD (%); NYHA class = New York Heart Association classification; peak $\dot{V}O_2$ = peak oxygen consumption; $\dot{V}E/\dot{V}CO_2$ = ventilation/carbon dioxide production slope; *P<0·05, **P<0·005, ***P<0·0005 detraining vs training.

Table 3 Effect of physical training on autonomic tone, as described by neuro-humoral factors and heart rate variability indices

Variable	Detraining	Training	n
Noradrenaline			
rest (pg . ml^{-1})	508 ± 263	393 ± 179*	43
peak (pg . ml^{-1})	1111 ± 801	1754 ± 1535*	43
Adrenaline at rest (pg . ml^{-1})	93·20 ± 133·64	42·45 ± 29·21	11
PRA (ng . ml^{-1} . h^{-1})	14·46 ± 16·66	12·72 ± 13·62	11
Aldosterone (pg . ml^{-1})	203·10 ± 104·08	201·25 ± 123·59	11
ANP (pg . ml^{-1})	259·41 ± 94·55	240·46 ± 129·14	11
Heart rate variability			
SD (ms)	35·86 ± 12·36	40·43 ± 13·29*	57
LF (ms^2 . min^{-1})	207·54 ± 242·94	339·85 ± 314·98*	57
HF (ms^2 . min^{-1})	85·54 ± 101·97	160·61 ± 153·78**	57

n = number of patients; PRA = plasma renin activity; ANP = atrial natriuretic peptide; SD = standard deviation; LF = low frequency component; HF = high frequency component; *P<0·05, **P<0·005 training vs detraining.

reduced non-significantly, but as the peak heart rate was increased after training, a significant increase in chronotropic response was reported (+13·3 ± 23·5 beats . min^{-1}, +38·5 ± 110·6%, P<0·0005). Systolic blood pressure did not change at rest but increased at peak exercise (+12·8 ± 28·3 mmHg, +6·0 ± 19·8, P<0·05) (Table 2).

Influence of patients' characteristics on training effects

Patients of all NYHA classes improved after training, although in the more severely compromised patients there was a reduced absolute training effect (peak $\dot{V}O_2$: +1·3 ± 2·5 ml . kg . min^{-1} in class III, vs +2·4 ± 3·7 in class II, P<0·05; exercise duration: +1·3 ± 1·4 min in class III, vs +2·1 ± 2·1 in class II, P<0·05). But in percentage terms, the improvements in peak $\dot{V}O_2$ and exercise duration were similar in NYHA class II and III (peak $\dot{V}O_2$ +12·1 ± 23·1% vs +14·4 ± 20·3%, exercise duration +16·5 ± 23·1% vs +18·7 ± 21·1% respectively, P = ns). No differences were observed in compliance to cycle ergometer training between class III and the other patients (82·0 ± 12·1 vs 89·1 ± 17·1% respectively, P = ns).

Sixty-eight patients (53·9%) responded to rehabilitation, defined as a >10% increase in peak $\dot{V}O_2$[12]: they had a left ventricular ejection fraction slightly higher than the 'non-responder' patients (26·5 ± 8·8 vs 23·3 ± 8·8%, P = 0·05) but no other baseline patient characteristics differentiated the two groups.

Although female patients were few in number (n = 9), they had a significant improvement in peak $\dot{V}O_2$ (+2·7 ± 2·7 ml . kg . min^{-1}, P<0·001): this improvement was not significantly different to that observed in males. Physical training improved exercise tolerance in subjects with non-sustained ventricular tachycardia on 24 h ECG monitoring (n = 31), although to a certain extent compared to those with no ventricular tachycardia (peak $\dot{V}O_2$ +1·4 ± 3·8 vs +2·8 ± 3·7 ml . kg . min^{-1}, respectively, P<0·01). Also the older patients (>70 years, n = 14) trained free from complications, with a significant benefit in terms of symptoms (NYHA class from 3·1 ± 0·6 to 2·6 ± 0·5, P<0·01), but with

little improvement in terms of exercise duration (+0·8 ± 1·2 min, P = ns) or peak $\dot{V}O_2$ (+0·2 ± 1·3 ml . kg . min^{-1}, P = ns). Patients under different pharmacological therapies did not show any significant difference in the training response.

Aetiology and training

The patients with ischaemic heart failure showed less of an improvement in peak $\dot{V}O_2$ in comparison with non-ischaemic patients (+1·5 ± 2 3 vs +3·1 ± 5·2 ml . kg . min^{-1}, P<0·05), but a similar improvement in exercise duration and NYHA class. However, the two groups of patients were not similar: the ischaemic patients, with respect to the non-ischaemic ones, were older (61·9 ± 7·9 vs 55·2 ± 9·3 years, P<0·0005), had lower baseline exercise tolerance (peak $\dot{V}O_2$: 14·2 ± 1·3 vs 18·9 ± 6·3 ml . kg . min^{-1}, P<0·0001) and were more symptomatic (NYHA class: 2·56 ± 0·51 vs 2·21 ± 0·56, P<0·002).

Autonomic nervous system measures and training

Training reduced all the neurohumoral factors at rest: noradrenaline, adrenaline, aldosterone, atrial natriuretic peptide, plasma renin activity and aldosterone. The plasma noradrenaline level at peak exercise, conversely, increased after training. All the heart rate variables improved after training, with significant increases in the standard deviation of RR interval and both low frequency and high frequency fluctuations (Table 3).

Correlations of baseline factors and improvement in exercise performance after training

To elucidate the factors most likely to be related to an improvement in exercise capacity after training, simple and multiple linear regression analyses were performed for baseline parameters against the percentage improvement in exercise time or peak $\dot{V}O_2$; these two variables were significantly correlated, as expected (r = +0·5, P<0·001), and either could substitute in the regression equations.

None of the baseline characteristics was significantly correlated with the improvements. In particular, age showed no relationship with the training response; there was no evidence for the more severely affected patients with lower initial left ventricular ejection fractions or lower peak $\dot{V}O_2$ having a different response to training. Also, an initially more abnormal autonomic control (as reflected by neurohumoral or heart rate variability indices) did not differentiate between chronic heart failure patients with better or worse training responses.

Correlations of training-induced changes and improvements

We evaluated the training-induced changes that correlated with the improvement in exercise performance (percentage increase in $\dot{V}O_2$) or symptoms (percentage increase in NYHA class). An expected correlation was present between symptomatic improvement (NYHA class reduction) and exercise tolerance (peak $\dot{V}O_2$ increase) (r = 0·5, P<0·01).

The percentage increase in chronotropic response showed the highest value of correlation with the improvement in exercise performance (r = 0·6, P<0·0001) (Fig. 1); but significant correlations were also seen with percentage increases in peak exercise systolic pressure and in noradrenaline at peak exercise (both r = 0·5, P<0·01), with the reduction in resting plasma renin activity, and in aldosterone (both r = 0·4, P<0·05), and the increase in heart rate variability standard deviation (r = 0·5, P<0·01): all significantly correlated with the improvement in exercise performance (Fig. 1).

The changes in symptoms (NYHA class) correlated with the percentage increases in resting heart rate variability standard deviations and the high frequency component (r = 0·5, p<0·01) and with the reduction in resting heart rate and hormones, i.e. atrial natriuretic peptide, plasma renin activity, aldosterone (r = 0·4, P<0·05); a significant correlation was also present with increases in systolic pressure at peak exercise (r = 0·5, P<0·01).

Effect of differences in the training protocol

There was a significant positive correlation between the training effect and the duration of the exercise programme: the peak $\dot{V}O_2$ improvement after the 16 weeks' programme was higher than after the 6 weeks' programme (+2·6 ± 3·0 vs +0·3 ± 3·1 ml . kg . min^{-1}, P<0·05). The group of patients who responded to rehabilitation trained for a significantly longer time period than the non-responder patients (10·5 ± 3·4 vs 9·2 ± 3·0 weeks, P<0·02).

The combination of cycle ergometer training with calisthenic exercise was more beneficial in terms of improvement in peak $\dot{V}O_2$ compared to cycle ergometer training alone: +2·7 ± 4·2 vs 1·2 ± 2·0 ml . kg . min^{-1}, P<0·01. The different mode of training (i.e. home-based or hospital-based or combined) did not affect the benefit in terms of exercise tolerance; however, the patients' symptoms improved more in the combined home and hospital-based than in the hospital-based only training programme (NYHA class +0·53 ± 0·35 vs 0·12 ± 0·35, P<0·01).

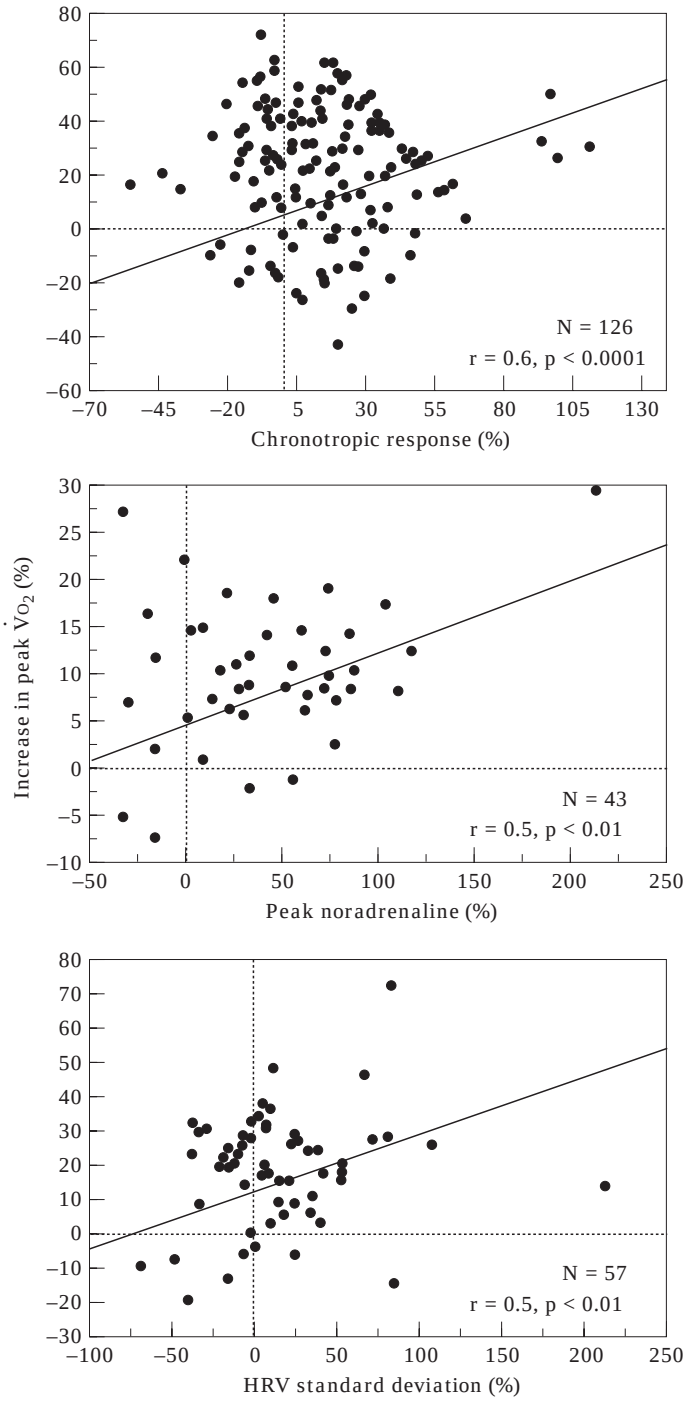

Figure 1 **Significant relations between training induced increase in peak oxygen consumption (peak $\dot{V}O_2$) and training induced percentage changes in chronotropic response, plasma noradrenaline at peak exercise, and standard deviation of heart rate variability (HRV).**

Discussion

This overview supports previously published studies and the growing literature on exercise and muscle physiology in chronic heart failure[9–11]. Moreover the safety of a moderate physical training programme is confirmed. Thus, earlier prohibition and concerns not withstanding[30], appropriately selected chronic heart failure patients can be safely entered into exercise training programmes. Significant improvements in exercise

tolerance and symptoms can be anticipated. The high compliance to the training programmes observed in our trials is consistent with the symptomatic benefit coming from encouraging chronic heart failure patients to participate actively in their own treatment. The clinical benefit reported in terms of exercise tolerance are quantitatively similar to those achieved with most effective drug treatments. ACE-inhibitor therapy has been shown to induce increases in peak $\dot{V}O_2$ of up to 2 ml . kg . min^{-1}, and exercise time of up to 1·5 min[7,31]. Complex surgical techniques such as dynamic cardiomyoplasty or cardiac transplantation have not been proven to yield significant improvements in exercise tolerance or quality of life in large controlled randomized trials and both medical and surgical treatments for chronic heart failure are very expensive. Physical training as part of chronic heart failure rehabilitation improves peak $\dot{V}O_2$ up to 2 ml . kg . min^{-1} and exercise duration more than 1·5 min, both worthwhile effects. A partially home-based training programme, with reduced cost, could have beneficial impact on the social cost of the syndrome and the frequency of hospitalization. Furthermore, as the chronic heart failure patients are significantly limited functionally, even a small increase in exercise tolerance could dramatically reduce patients' dependency. Thus in an increasingly competitive health care climate, training could be a highly cost effective resource in chronic heart failure.

Patients' characteristics

This overview confirmed that most patients with stable chronic heart failure in NYHA classes II and III could enter a physical training programme without any major side effects. Both female and male patients with coronary artery disease or chronic heart failure of other aetiology can obtain benefit. Age itself is not a contraindication, with patients older than 70 years able to train with a consequent effect on symptoms (NYHA class), although with less benefit in terms of exercise tolerance. The presence of non-sustained ventricular arrhythmias, a common accompaniment of the chronic heart failure syndrome, did not preclude a training effect and therefore may not be a contraindication to physical conditioning, although specific safety studies in this group of patients are essential.

Perhaps is was not surprising that a lesser improvement in exercise tolerance was seen in patients with more severe chronic heart failure (NYHA class III) because of the more depressed capacity to train. But in percentage terms, the improvements in peak $\dot{V}O_2$ and exercise duration were similar in NYHA classes II and III, confirming that even in high-risk chronic heart failure patient's training could give beneficial effects[9]. Other estimations of severity, such as left ventricular ejection fractions or plasma noradrenaline did not significantly predict the training-induced benefits.

In agreement with another study[13], patients with ischaemic heart failure showed a lower improvement in peak $\dot{V}O_2$ in comparison with patients with idiopathic dilated cardiomyopathy (but not in exercise duration or NYHA class). In our study this finding could, at least partially, be attributed to their worse clinical condition at baseline, and to the fact that they were older. All patients were on optimal stable pharmacological therapy: the choice of drug therapy did not affect the benefits of physical training. In particular, physical training produced an improvement in exercise tolerance whatever the drug therapy at baseline. Previous studies from our group[7] reported a training effect to be additive to the influence of the ACE-inhibitors, suggesting that the long-term effects of these drugs may be at least partially independent of physical conditioning effects.

Autonomic nervous system

All humoral and heart rate variability indices indicated a partial reversal of the autonomic disbalance after training, with a reduction of sympathetic overactivation: noradrenaline, adrenaline, aldosterone, atrial natriuretic peptide, plasma renin activity, aldosterone were all significantly reduced. The increased plasma noradrenaline level at peak exercise is consistent with an increase in autonomic responsiveness, a finding that would fit with the enhanced chronotropic responsiveness and systolic blood pressure response to exercise. The increase in heart rate variability indices, and in particular the total variability (standard deviation of RR interval) and its high frequency component, supported an improvement in vagal tone previously observed[5,6].

Ventilatory effects

The $\dot{V}E/\dot{V}CO_2$ slope during exercise has been used as a marker of the severity of chronic heart failure[32], and this has been significantly reduced after physical training: it reflects a reduced minute ventilation and improved ventilatory control. This finding may help to explain the improvement in reduced breathlessness, allowing a greater respiratory reserve. It is not possible to rule out that the physical rehabilitation programmes performed by our study population could also have induced respiratory muscle training, which has been shown to reduce dypsnoea on exercise[33]. A change in ventilation-to-perfusion matching in the lung with reduced dead space may be a potential factor in respiratory changes after training[34], but in the absence of any suggestion of enhanced cardiac (left or right ventricular) function this would be difficult to explain.

Correlates of improved exercise performance

No humoral, autonomic or haemodynamic factor was correlated with the improvement in exercise capacity. In

other words, it was not possible to identify which patient might benefit the most from exercise rehabilitation on the basis of the clinical characteristics at baseline.

The lack of correlation between an index of left ventricular function, ejection fraction, and the training effect is not surprising, as it has been demonstrated that exercise capacity correlates poorly with indices of central haemodynamic function[35]. Exercise intolerance with abnormal pulmonary function is secondary to changes elsewhere[9,34]. It has been demonstrated that the physical training improvements are closely correlated with peripheral changes: increases in skeletal muscle oxidative capacity, increases in leg blood flow with reduction in femoral venous lactate[9], improvements in endothelial function[10], and ultrastructural morphology of the skeletal muscles[11]. The effects of these changes might be direct and/or may be mediated by a reduced activation of muscle afferents (ergoreceptors), sensitive to the metabolic state of the muscle which control ventilatory, haemodynamic and respiratory responses to exercise[36].

Our results differ partially from the recent report of Wilson and colleagues[12] who found that training effects were less pronounced in patients with an abnormal cardiac function, and an abnormal cardiac output response to exercise. In the present overview, the patients who responded to rehabilitation had a slightly higher left ventricular ejection fraction than non-responder patients. However, the factor that seemed to play a major role in the response to training was the duration of the programme: the responder group trained for a significantly longer time than the non-responder patients. Moreover in Wilson's study the training programme was more aggressive: a more tailored programme may have benefited these patients.

Significant correlations were present between increases in humoral factors (plasma renin activity, aldosterone), autonomic indices (heart rate variability standard deviation) and improvements in exercise tolerance and symptoms. This study cannot tell us the precise mechanisms of the training-induced improvements in exercise capacity, but as the changes in ventilation heart rate, and neurohumoral factors would allow the same work to be achieved at a lower level of sympathetic drive, heart rate, myocardial oxygen requirement and minute ventilation, it is plausible that reserve exercise capacity could be enhanced.

Influence of the length of the training programme

Previous studies have demonstrated the benefits of short-term exercise training in chronic heart failure patients[5,7]. There has been a reluctance to prescribe long-term exercise in this syndrome: the ominous nature of chronic heart failure syndromes have favoured a cautious approach. Two exercise training reports suggested that subsets of heart failure patients (those with lower ejection fractions and ST segment depression on exercise testing[37] and those with extensive anterior myocardial infarction[38]) might not benefit from exercise training: however, both studies were non-randomized and did not consider patients in chronic stable conditions. A randomized study observed that patients post large anterior myocardial infarction with poor left ventricular function have benefited from long-term physical training[39]. More recently it has been observed that the functional gains of training are positively influenced by the duration of the programme: they are higher after 12 weeks' than after 6 weeks' exercise[15] and also higher after 24 weeks' than after 12 weeks'[13]. These gains can be maintained over a year of continuing exercise in chronic heart failure, although evaluated in a non-randomized trial[14].

The significant correlation between training effect and duration of exercise training observed in this overview confirms the safety and the benefit of long-term physical rehabilitation in chronic heart failure patients with stabilized clinical conditions. The potential risks and beneficial effects in terms of prognosis (hospital stay and mortality) however, need to be evaluated in larger controlled randomized trials.

Influence of the training protocol

Several unsolved points are present concerning the more appropriate training protocol in chronic heart failure. Different studies have used different programmes. Differences exist in terms of the number of exercise sessions/week proposed (from 2 to 7 days/week), the duration of each exercise session, and the type and intensity of exercises. Preliminary reports proposed a combination of walking, jogging and cycling[4,16,17]. Others have proposed single arm exercise[18], but the first controlled trials showed the safety of the cycle ergometer[5–7]. Subsequently, in controlled studies the effectiveness of other exercise protocols have been shown, such as bench exercise[19], aerobic progressive walking[14], combined treadmills, cycling, rowing machines, arm ergometers[13], knee extensor training[20], calisthenic and walking exercises[9]. Therefore it is not surprising that this overview has demonstrated that a more comprehensive training programme involving both cycle ergometer and calisthenic exercise is more beneficial than cycle ergometer training alone. The potential benefit of other exercise programmes, such as strength training which affects muscle mass, may also be considered in this syndrome, although less experience is available[3].

It has been hypothesized that a low level (corresponding to 40–50% maximal $\dot{V}O_2$[15,21,22]) or more localized training (such as one- or two-legged knee extensor training)[23] programme may be more advantageous than the programme at the conventional workload (corresponding to 70–80% maximal $\dot{V}O_2$), because the former could reduce the risk of left ventricular dilatation minimizing the ventricular wall stress. This hypothesis is reported in small studies, while larger trials in ischaemic patients with left ventricular dysfunction

that did not find any deterioration in cardiac function[39] warrants further investigations: no study has specifically investigated the long-term effects of different levels of exercise training in chronic heart failure. Our overview also provided no data on left ventricular function after training. However, Meyer *et al*. have observed that interval exercise training at different modes and levels (50%, 70% and 80% of predetermined maximal capacity) could all be beneficial in chronic heart failure[24].

Unclear data have been published on whether a home-based exercise programme is as safe as a hospital-supervised training protocol. Coats *et al*. were the first to show the beneficial effect of a home-based exercise protocol in chronic heart failure[5]. In this overview, the reported higher symptomatic benefit after combined home and hospital-based training programmes may reflect improved patient compliance with the protocol performed both at home and in the hospital: however, complete data concerning the compliance of all patients were not available.

Study limitations

Our study leaves many unsolved questions concerning the adequate training protocol for chronic heart failure patients, as discussed above: although it gives some insight, it is still unclear what level, duration, and intensity of exercise should be prescribed.

Reduced heart rate variability, baroreceptor sensitivity and increased plasma noradrenaline levels have all been shown to be independent predictors of increased mortality in chronic heart failure[40–42]. The improvement in exercise tolerance and quality of life associated with physical fitness have been associated with lower incidence of coronary artery disease and death in normals[43,44]. The alterations in autonomic function (although obtained on a small sample of subjects) and the improvements in exercise tolerance associated with physical training naturally leads to speculation as to whether the natural history of chronic heart failure may be favourably altered by this approach. This overview cannot answer this question. A clinical trial of adequate size and duration is needed to address mortality effects.

We did not measure invasive haemodynamics during exercise to estimate peak cardiac output, and it may be that a purely 'cardiac' limitation, as opposed to 'peripheral' limitation to exercise, may be an adverse predictor of training effects[12]. The fact that we found a fairly uniform increase in exercise tolerance suggests that this effect may be limited, perhaps because of the long period of clinical stability in our patients prior to study entry.

Conclusion

A tailored, moderate, home-based cycle ergometer plus calisthenic exercise training programme seems safe and beneficial in a large cohort of heart failure patients, with similar benefits in a variety of conditions and hospital settings. However, there are still many unsolved questions concerning the safety and efficacy of long-term exercise, and the most suitable training protocol. In order to make the cardiac rehabilitation exercise programme a customary option in chronic heart failure, as after myocardial infarction or coronary artery bypass surgery, there remains the need for a large controlled prospective trial to assess the value of medically prescribed exercise training in this syndrome: we hope this report may help stimulate this endeavour.

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