Exercise Training in Heart Failure: When?

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The cardinal symptoms limiting exercise in patients with chronic heart failure (CHF) are fatigue and/or dyspnea.Conventionally, it has been taught that both are the direct result of reduced cardiac output. Fatigue was thought to arise from the impaired cardiac pumping capacity delivering inadequate amounts of oxygen to the exercising muscle so that there is a buildup ofproducts of anaerobic metabolism within the muscle. Dyspnea was thought to arise from the effects of impaired cardiac function increasing left atrial pressures and thereby pulmonary venous pressures and producing pulmonary congestion. This explanation formed the basis of the subdivision of heart failure into forward and backward heart failure symptoms. Several recent lines of evidence, however, have questioned these assumptions. Persistent vasoconstrictor drive, endothelial dysfunction, and a wide array of structural and functional abnormalities of skeletal muscle have all been described as being better able to explain fatigue in CHF [1]. Dyspnea appears to be related to enhanced ventilatory effort rather than pulmonary congestion in most well-treated nonedematous patients [2]. This may in particular be related to augmented reflex control systems such as the arterial chemoreflexes and the muscle ergoreflexes (metaboreflexes) [3,4]. Furthermore, even the differentiation between fatigue and dyspnea may be artificial in many patients, since as either symptom can occur with subtle alterations in the exercise testing procedure, and in many patients a sensation of exhaustion may have elements of both [5]. The cause of the perceptions of fatigue and dyspnea may arise from similar sensory afferents from the abnormal muscle of chronic heart failure patients. For all these reasons, attention has turned to the role of peripheral manifestations of chronic heart failure and in particular to whether exercise training programs could reverse some of these abnormalities and thereby improve the symptoms and exercise tolerance of the patient with CHF.

This special issue reviews some of the evidence for a role for exercise training, concentrating on particular aspects of the use of training as a therapeutic option in the clinical setting. This article will concentrate on the timing of exercise in the management of patients with left ventricular dysfunction and chronic heart failure throughout their clinical course.

Beneficial Effects of Exercise Training in Cardiac Patients

Regular physical exercise has been repeatedly shown to be associated with a reduced lifelong risk of developing coronary artery disease (CAD) [6–8]. The mechanisms are not known, but regular exercise is associated with many ancillary preventive aspects such as increased insulin sensitivity; reduced obesity, fibrinogen levels, and blood pressure; enhanced vagal activity and diastolic function of the heart; and improved lipid profiles. All or any of these factors may confer protective effects on the heart and cardiovascular system. With these known and well-established benefits, it is government policy in most developed countries to enhance physical activity levels of the healthy population, and it is thought that these benefits will be most clearly evident in populations at higher risk for developing CAD. The first evidence of CAD is frequently the onset of myocardial infarction (MI) and the benefits of an exercise component as part of comprehensive cardiac rehabilitation are now well established [9–12]. In patients who present with angina rather than an MI, exercise training has been shown to enhance angina thresholds and improve quality of life in addition to the beneficial effects on coronary blood flow via enhanced collateral development and improved myocardial perfusion [13]. These effects mean that exercise training should be recommended for anyone at high risk of CAD or with established CAD, be it stable angina or post-MI, provided that he or she is free of specific contraindications to exercise training. One such contraindication was formerly said to be significant left ventricular dysfunction or a history of heart failure. More recent work has shown, however, that these restrictions may have been too harsh.

Exercise Training in Chronic Heart Failure

We have known for many years of the benefits of an exercise component in cardiac rehabilitation. It was...
felt initially that significant left ventricular impairment was a contraindication to participation in such programs. In fact, in heart failure there was a vogue for and reports of the beneficial effects of prolonged bed rest [14]. Until the late 1980s, avoidance of physical exercise was the standard recommendation for all patients suffering from heart failure. It was against this background that a few challenging reports emerged from several groups showing that, in rehabilitation programs, even patients with significantly impaired left ventricular function could increase their exercise tolerance [15–17]. In these studies, there was no detectable deterioration in left ventricular function. It was not until the end of the decade that reports were published showing that physical training could increase exercise capacity in patients with chronic heart failure. Sullivan and colleagues [18,19] found that patients with severe left ventricular dysfunction, some of whom had previously suffered heart failure, improved their maximal exercise performance after a prolonged regime of physical training. They demonstrated both an increased blood flow to exercising muscle and an increased ability of skeletal muscle to extract oxygen from the nutritive blood flow. Ventilatory function was also improved, with a reduction in the respiratory exchange ratio at submaximal exercise and a delay in the anaerobic threshold. These studies showed no improvement in exercise cardiac output, so it appeared that the training-induced benefits were mainly due to peripheral adaptations.

The beneficial effects of training were confirmed in a controlled crossover trial in 11 subjects with stable class II–III chronic heart failure [20]. These were carefully selected patients with chronic heart failure who could exercise without serious ventricular arrhythmias and in whom there was no other medical condition limiting exercise tolerance. After baseline evaluation and familiarization with laboratory procedures, all patients performed eight weeks of exercise training and eight weeks of exercise avoidance in a randomized crossover study. The training regime led to an approximate 25% increase in exercise tolerance and peak oxygen consumption. There was also a significant reduction in questionnaire-rated symptoms attributable to heart failure and a coincident increase in both the extent and ease of performing daily activities. Since these early reports, a large number of trials of similar design have confirmed these benefits and detailed a long list of useful ancillary effects of training in a heart failure population (see Table 1).

In the decade following these first reports, there have been a profusion of small trials and a long list of impressive physiological gains that could be achieved. These included increased peak oxygen consumption [21–25], an increase in peak cardiac output (in some [21] but not all trials), and improvement in the autonomic control of the circulation [21,26]. More recent reports have documented an increase in endothelial function [27], in skeletal muscle biochemical [28,29] and histological [24,30] characteristics, and improvements in patients’ perceptions of their quality of life and symptom severity. These training benefits have been shown against a background of increasing interest in and realization of the importance of secondary peripheral manifestations of the syndrome of chronic heart failure [31]. The importance of neurohormonal overactivity has been recognized for a decade, but the importance of other changes such as altered and wasted skeletal muscle and a host of major metabolic disturbances in chronic heart failure are only just being appreciated [32].

The Mechanisms of Training Effects in Chronic Heart Failure

Left ventricular function

Despite earlier fears, in no study of training in CHF published to date has there been any significant deterioration in resting left ventricular function. Cardiac output is either unaltered [19] or shows a small increase [21] after training. Left ventricular filling pressures are not changed [19]. Training can, however, produce reductions in peripheral vascular resistance and heart rate at submaximal and peak exercise [21] so that the loading conditions of the heart are altered. It is difficult, therefore, to exclude any change in the inotropic reserve of ventricular performance, but given the fairly uniform increase in exercise capacity seen in the training studies, it seems unlikely that there is any significant reduction in left ventricular performance. A study by Jugdutt et al. [33] in patients early after a large myocardial infarction showed some left ventricular enlargement in a subset of patients with preexisting left ventricular asynergy, but this study used a vigorous training regime early in the healing phase after infarction and did not have a properly randomized control group as a comparison. The results of these authors have not been confirmed in patients with stable chronic heart failure. Better-designed studies in patients with large Mls have shown that progressive left ventricular remodeling is a feature of the initial

Table 1. Recognized benefits of training in chronic heart failure

| Benefit | Description |
|---------|-------------|
| Exercise tolerance increased |
| Symptoms improved |
| Ventilation reduced |
| Skeletal (and respiratory) muscle function improved |
| Vascular function (large and small arterial) improved |
| Abnormal autonomic function partially corrected |
| Neurohormonal activity reduced |
| Ergoreflex activity reduced |
| Diastolic function improved |
| Ventricular remodeling slowed |
| Myocardial perfusion enhanced |
insult rather than of exercise training [34]; in fact, the ELVD study showed a significant improvement in left ventricular remodeling attributable to training participation [35]. It may be that a chronic reduction in sympathetic tone could improve the remodeling process, and this outcome may be more important in the long term than the short durations of exercise necessary to achieve the training effects.

**Ventilatory control**
Minute ventilation and the slope relating ventilation to carbon dioxide production are both reduced by exercise training [18]. These features of heart failure patients are likely to be associated with early dyspnea and have recently been shown to be predictive of a poor prognosis independently of conventional markers of disease severity. Training is associated with a reduction in lactate release and respiratory exchange ratio, indicating improved submaximal exercise performance [18,21]. Apart from the improvements in skeletal muscle function described below, it is not known what factors underlie these changes, although beneficial effects on chemoreflex function is a possibility.

**Autonomic function**
Sympathetic tone is reduced by training, as shown by a reduction in resting noradrenaline spillover, an increased heart rate variability, and a shift in the relative preponderance of low- and high-frequency heart rate variability rhythms as detected by power spectral analysis [21]. This latter technique has suggested that in heart failure subjects, training can increase vagal activity and reduce cardiac sympathetic tone [21].

**Skeletal muscle**
Single-limb training has been shown to partially correct the exercise metabolism of arm skeletal muscle in patients with heart failure. This outcome was shown despite no systemic training effects [28]. Leg muscle metabolism has also been shown to improve as part of an endurance training regime utilizing bicycle exercise [36]. In an animal model of heart failure, similar metabolic abnormalities have been corrected by training [37], with restitution of muscle oxidative enzymes. These changes may be the basis for the reduction in activity of the muscle ergoreflex activation seen in heart failure patients after localized muscle training as demonstrated by Piepoli et al. [4].

**Endothelial and vascular function**
Hornig and others have demonstrated improvements in endothelial function after exercise training in CHF, and this improvement may be a significant mechanism of enhanced exercise performance in some patients [27].

**Other noncardiac manifestations of heart failure**
Little information exists as to whether training can prevent or correct skeletal muscle wasting. The effects on renal blood flow and function have also not been assessed. The levels of circulating neurohormones and the function of beta receptors and postreceptor pathways are also areas where training may be producing some of its effects, but insufficient data have as yet been accumulated.

**Safety of Training in Heart Failure**
Despite the list of benefits described above and the growing list of published reports with improved outcomes, some caution is needed in the use of exercise therapy in patients with heart failure. Training can have potential adverse effects if sufficient patient assessment is not undertaken (see Table 2). Of these risks, some are predictable, such as the possibility of muscular injury. Some should always be considered, such as the risk of exercise-induced arrhythmias, and for this reason multiple supervised exercise sessions should be completed before the patient is encouraged to exercise at home without monitoring and resuscitation facilities. Lastly, the possibility for a short-term need for enhanced diuretic dose should be considered because training can increase blood volume, and in a patient with critical heart or renal function, this increase can lead to clinically evident fluid retention.

Training may not be equally effective in all patients with CHF. John Wilson described a proportion of his patients either unable to complete an exercise program or achieving no increase in exercise capacity from so doing [38]. These patients seemed to be those with limiting cardiac output rather than those limited by secondary changes in the periphery, such as impaired peripheral vasodilatory capacity or impaired skeletal muscle function. This distinction may be quite important, since as training does appear to achieve many of its beneficial effects through peripheral mechanisms.

**Training as a Standard Therapeutic Option for Chronic Heart Failure**
When to recommend training is an important question. To date, all trials have trained only stable patients, and hence we can at present only recommend training after optimization of medical therapy and stabilization. In

| Table 2. Potential hazards of aggressive exercise therapy in chronic heart failure |
|---------------------------------------------------------------|
| • Arrhythmias/sudden death                                    |
| • Adverse left ventricular remodeling                        |
| • Fluid retention                                             |
| • Muscular injury                                             |
early cases of cardiomyopathy, especially if there may be an active myocarditic process, exercise should be postponed for full diagnostic evaluation and therapeutic stabilization. In addition, several conditions remain contraindications to exercise training. These include uncorrected obstructive valvular disease, especially aortic stenosis; active myocarditis, either viral or autoimmune; hypertrophic cardiomyopathy; exercise-induced, high-grade ventricular arrhythmias; and manifest decompensated cardiac failure. These conditions should remain contraindications to exercise therapy.

Three major questions remain unanswered despite the wealth of evidence we have obtained over the last two decades:

- whether the training effects could be maintained long term;
- whether training is practicable in multiple medical settings and in routine practice; and
- whether training would have beneficial effects on mortality or morbidity.

We have published our own experience of training in multiple units across several European countries with different health care systems and have found that these differences were of lesser importance compared to factors such as the duration of training or the setting (in-hospital only, out-of-hospital, or a combination). None of the patient factors studied (etiology, NYHA class, left ventricular ejection fraction, or medication) appeared to predict the training response [39].

The literature to date includes about 500–600 patients reported as having taken part in randomized trials of exercise training in the setting of chronic heart failure. Recent conference reports have been presented, however, of randomized trials of approximately 100 patients each, and two of these reports appear to show reduced mortality and hospitalization rates reaching statistical significance. We await the full reports eagerly. With these trials and the as yet unpublished EXERT trial from Canada [40], the experience on training in CHF is growing at a rapid pace. What is sorely needed now is definitive information concerning the impact of this treatment option on mortality and worsening of heart failure. The emerging results give encouragement that we may now have sufficient trial data upon which to make estimates on possible mortality effects of training in similar groups of patients. Furthermore, it now appears that a mortality trial of this nature is both possible and urgently needed. Such a trial has been proposed, and we hope that a mortality trial of this nature is both possible and urgently needed. Such conditions should remain contraindications to exercise therapy.

Summary

Substantial and reliable effects of training in carefully selected and well-evaluated patients with heart failure have now been established. Many questions as to the most appropriate setting for this training and the crucial details of patient selection and continuation strategies remain unanswered, as do questions concerning the search for a positive outcome effect and the economic effects of training. Despite these reservations, believe it appears that we can now say that training for heart failure has a definite role and an established place in the treatment options for CHF. The question “When?” can be best answered as follows: “When things are stable—either after MI or chronically.”

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