

The state of exercise training: A need for action

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Although our ability to treat heart failure continues to expand with improved medical therapies, there remains a need to identify new strategies to improve outcomes in this growing patient group. Heart failure affects 5 million patients and is the only cardiovascular condition growing in prevalence (American Heart Association, 2000). Industry continues to study new therapies to treat patients with heart failure, including endothelin antagonists, vasopeptidase inhibitors, cytokine antagonists, biventricular pacing, and external counterpulsation, but there is a need to explore therapies not promoted by private industry, such as exercise training.¹ The high morbidity and mortality rates associated with heart failure despite optimal pharmacotherapy and the increased prevalence of patients with heart failure underscores the importance of research into novel treatment strategies such as exercise training.²

Patients with congestive heart failure (CHF) have a poor quality of life compared with patients with other chronic diseases.³ A major cause of decline in quality of life is reduced exercise tolerance. As the disease progresses, patients become more incapacitated and deconditioned, unable to perform simple tasks without becoming dyspneic and fatigued. Exercise intolerance in patients with CHF is a result of several factors, including poor left ventricular function and abnormal peripheral factors such as blood flow, skeletal muscle changes, and ventilatory dysfunction. The decline in exercise capacity is of concern because exercise capacity, as measured by maximal oxygen consumption on an exercise test, is considered a strong predictor of survival.^{4,5}

In this issue of the *American Heart Journal*, McKelvie et al⁶ report their findings from a randomized control trial of exercise training and usual care versus usual care. One hundred eighty-one patients with New York Heart Association class I to III symptoms and a left ventricular ejection fraction <40% were recruited and followed for at least 12 months. The investigators modeled the intervention on traditional cardiac rehabil-

itation with the initial 3 months of exercise training supervised in a rehabilitation program and the final 9 months of training at home on an exercise cycle provided by the study. In addition to the aerobic training, patients in the exercise arm also performed resistance training with weights.

The exercise intervention did provide some benefit to the patients in the training arm of the study. Patients improved their exercise test performance compared with their baseline results and compared with patients in the control arm. They improved their muscle strength. There was a slight improvement in the quality of life score. Unfortunately, a consistent finding in this study was the loss of a training effect after the initial 3 months of supervised training. By the end of 12 months of follow-up, there was essentially no difference between patients receiving the intervention arm and those in the control arm.

The loss of a training effect suggests that there is a dose response to training that requires a certain intensity to achieve a detectable benefit. Dose can be quantified by either the number of times a patient trains or the amount of training each patient performs per training session. We know that patients achieve a training effect when exercising at a moderate intensity.⁷⁻⁹ In the study by McKelvie et al, there was a significant drop-off on the number of times a patient exercised during the home-training portion of the study compared with the initial supervised training. The investigators attempted to improve training adherence by providing exercise equipment but did not provide other interventions such as behavior modification tools, follow-up phone calls, or adherence measurement tools such as a diary, heart rate monitor, or odometer. This may have been due to the investigators' focus on creating a real-world type of intervention. The decrease in dose is defined by the number of times training appears to have caused the loss of training effect.

Over the last 11 years, 14 randomized, controlled studies, including the current study, have evaluated exercise training in patients with stable heart failure.^{6,8-20} All of these studies were prospective, randomized designs involving patients with ischemic and nonischemic cardiomyopathy and New York Heart Association class II or III heart failure and did not include patients with a recent myocardial infarction. Except for one study that used resistance training, training involved bicycle ergometers or walking at 50% to 70% peak Vo_2 , 3 to 7 times per week. Training occurred both in a supervised setting and/or in the

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home. In all of these studies, patients in the training arm improved physiologic parameters such as resting heart rate, exercise duration, and peak oxygen consumption.

These studies, along with smaller nonrandomized studies, have provided evidence for a number of mechanisms by which exercise training could affect morbidity and mortality rates. Exercise training improves peak Vo_2 , a strong independent predictor of survival.^{4,21} Changes in peak Vo_2 over time have been shown to predict nontransplanted survival independent of changes in left ventricular ejection fraction.²² Exercise training improves autonomic dysfunction in patients with heart failure, including decreasing resting plasma norepinephrine levels, an independent predictor of survival in these patients.^{11,13,23} Consistent with the improvements in neurohormonal activation, exercise training improves heart rate variability (HRV), another predictor of survival.^{16,24-26} Derangement in HRV is a potential mechanism for sudden arrhythmic death, common in patients with heart failure.²⁷ Clinical therapies that reduce neurohormonal activation and improve HRV provide significant survival benefit to patients with heart failure.^{28,29} Although not found in the current study, exercise training has been found to improve 6-minute walk distance, which has prognostic value for patients with heart failure.^{30,31}

The critical question is, do these physiologic changes caused by exercise training translate into an improvement in morbidity and mortality rates? The correlation of improvements in these variables with mortality rate reductions has been inconsistent in heart failure research. In the V-HeFT II trial, enalapril had a greater reduction in mortality rate as compared with the combination of hydralazine and isosorbide, but ejection fraction increased to a lesser extent and Vo_2 max was lower in enalapril-treated patients than in those treated with hydralazine/isosorbide.³² The history of heart failure research provides many examples of a pharmacologic intervention improving a number of surrogate end points in early studies, only to subsequently show a detrimental effect on survival in larger mortality trials. Milrinone, epoprostenol, flosequinan, and vesnarinone initially produced promising results, on the basis of improved physiologic end points, but were ultimately shown to worsen survival in controlled mortality trials.³³⁻³⁸

All of the randomized studies of exercise training were underpowered to appropriately evaluate the outcome of death and morbidity. The study by Belardinelli et al⁹ randomly assigned 99 patients to either facility-based exercise training or to no exercise training. Exercise training improved quality of life, decreased hospital admissions (29% vs 10%, $P = .02$), and decreased cardiac death (40.8% vs 18%, $P = .01$). Kaplan-Meier analysis of event-free survival revealed a significant

benefit to training (log rank = 14.29, $P = .002$). The recent study by McKelvie et al, which randomly assigned 181 patients, found no significant differences between patients treated with exercise and patients in the control group for total deaths, the composite of total deaths or heart failure hospitalization, and the composite of total deaths or worsening heart failure.

It is not clear if, as the investigators of the current study have, that given the results of their study and the study by Belardinelli et al, exercise training for patients with heart failure should be considered safe. The safety of exercise training in patients with heart failure has not been established in large clinical trials. Exercise training causes a short-term increased risk of myocardial infarction and sudden death, possibly the result of platelet activation or coronary artery shear stress.³⁹⁻⁴¹ Compared with habitual exercisers, patients who were habitually sedentary are at a 100-fold increased risk for myocardial infarction and a 50-fold increased risk of sudden death. Given the high prevalence of ischemic cardiomyopathy as a cause of heart failure and the deconditioning that occurs with heart failure, patients with heart failure may be at significantly higher short-term risk for myocardial infarction and sudden death.

In the 14 studies of patients with stable CHF, 374 participated in exercise training. Of the 374 patients participating in exercise training, 55 had a serious cardiac event (14.7%), 22 of which were deaths (5.8%). The complication rate of exercise training for these highly selected patients with heart failure was a >7-fold increase for patients with heart failure during exercise testing (2%) and a very large increase from the safety data reported for all of cardiac rehabilitation (29 events for 51,303 participants).^{42,43}

In research, equipoise is the state of balance between knowing the results of a study will be positive or beneficial and knowing the outcome will be negative or without benefit. There is a true state of equipoise regarding exercise training as an intervention for patients with heart failure. The inadequacies of physiologic outcomes to serve as surrogate end points for death, the limited and conflicting information about clinical end points from previous single-center studies, the absence of reliable safety data, and the real potential for an increased short-term risk of myocardial infarction and sudden death are the fundamental reasons why exercise training has not been accepted as standard of care for patients with heart failure. The phase II studies of exercise training have been completed. As stated by the investigators of the study in this issue of the *American Heart Journal*, a larger, long-term randomized trial (a phase III study) is necessary to confirm the promising results of smaller studies.⁶ More than 20 years of heart failure exercise training research has progressed to the point where the next logical

step is a study designed to measure the clinically relevant end points of death, morbidity, and quality of life.

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