Improving Exercise Tolerance in Chronic Heart Failure

A Tale of Inspiration?

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Dyspnea and exercise intolerance are hallmarks of chronic heart failure (HF). Over the past 3 decades, the importance of aerobic exercise capacity as an index of functional status and a prognostic marker in chronic HF has become widely recognized. A landmark study by Weber et al. (1) published in 1982 proposed a new classification system of chronic HF severity, on the basis of measured peak oxygen consumption (Vo2). Many subsequent studies have documented a strong relationship between peak Vo2 and mortality in chronic HF patients. On the basis of the dismal survival in patients with a markedly reduced peak Vo2, a peak Vo2 <14 ml/kg/min became a major criterion for referral for possible heart transplantation (2). Despite the significant improvement in symptoms and survival observed with pharmacologic blockade of the renin-angiotensin and beta adrenergic systems, such drug therapy generally has little impact on exercise capacity (3,4). In contrast, aerobic training programs increase peak Vo2 by 15% to 25% in chronic HF patients, similar to the degree of improvement observed in normal individuals after such training (5).

Because both the quality of life and longevity in chronic HF are so strongly influenced by aerobic capacity, it is important to understand the factors that limit peak Vo2 in this disorder. Peak Vo2 is determined by the product of cardiac output (CO) (i.e., the central component) and arteriovenous oxygen difference (AVo2 diff) (i.e., the peripheral component) during exhaustive aerobic exercise. Although both peak CO and AVo2 diff are reduced in chronic HF, the dominant deficit is in peak CO (5,6). In Weber’s classification scheme, invasively determined peak CO/m2 ranged from a mean of 7.8 l/min/m2 in Class B patients (peak Vo2 16 to 20/ml/kg/min) to 3.0 l/min/m2 in Class D (peak Vo2 <10/ml/kg/min) (1). A modest reduction in peak heart rate contributes to the reduced CO, but the primary limitation to increasing CO during exercise is the blunted ability of the failing heart to augment stroke volume, due to reduced reserve of both preload and contractility (5,6).

Recent years, however, have witnessed increasing recognition of noncardiac limitations to exercise in chronic HF patients. Numerous studies have documented a myopathy of the skeletal muscle in this condition, characterized by reduced muscle mass and strength, with decreases in oxidative type I fibers, mitochondrial volume density, and oxidative enzyme activity (5,7,8). These myopathic changes along with impaired regulation of blood flow to exercising muscle (9) help to explain the blunted augmentation of AVo2 diff with aerobic exercise.

What role, if any, do the lungs play in the exercise intolerance of chronic HF? It is well known that ventilation is excessive for the work performed in HF patients, probably owing to a combination of increased physiological dead space and greater lactate production. The magnitude of this ventilatory excess during exercise, quantified by the ventilation/carbon dioxide production slope (VE/VC02), is now recognized to correlate with clinical HF severity and to predict outcomes, independent of peak Vo2 (10,11). This exaggerated ventilatory response, coupled with reduced lung compliance and possibly increased airway resistance, contributes to the sensation of excessive respiratory effort during exercise in patients with chronic HF.

An additional potential ventilatory limitation to exercise in chronic HF is weakness of the respiratory muscles themselves, best quantified by reduced maximal inspiratory pressure (PImax). In a study of 244 patients with systolic HF, mean PImax was reduced 28% compared with healthy control subjects and was a strong independent predictor of 1-year mortality (12). Although the precise etiology of this respiratory muscle dysfunction is unclear, diaphragm biopsies have demonstrated a variety of histological abnormalities, including type I fiber atrophy similar to that observed in limb skeletal muscle.

In a prior issue of the Journal, Dell’Ago et al. (13) randomized 32 patients with chronic systolic HF and inspiratory muscle weakness, defined by PImax <70% of predicted, to 12 weeks of inspiratory muscle training (IMT) 30 min daily or to a placebo IMT with no inspiratory load. The IMT group experienced a 115% increase in PImax, 17% increase in treadmill peak Vo2, 19% increase in 6-min walk, and 14% reduction in VE/VC02 slope, whereas these variables were unchanged in the placebo IMT group. The increase in peak Vo2 correlated well with the change in PImax (r = 0.62). Quality of life scores on the Minnesota Living With Heart Failure questionnaire also improved.

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the National Heart, Lung, and Blood Institute, Bethesda, Maryland. The views expressed in this editorial are those of the author and do not necessarily reflect those of the National Institutes of Health or the Department of Health and Human Services.
after IMT, and this effect was partially maintained at 1-year follow-up.

In the current issue of the *Journal*, investigators from this same laboratory examine the changes induced by a 4-week IMT program (of identical intensity and session frequency as in their previous study) on resting and exercise limb blood flow in a new group of 18 chronic HF patients with inspiratory muscle weakness as defined in the preceding text (14). Before IMT, the HF patients experienced greater reduction in resting calf blood flow and a blunted rise in forearm blood flow response to rhythmic handgrip exercise during inspiratory muscle loading compared with 10 healthy control subjects. After only 4 weeks of IMT, HF patients demonstrated hypertrophy of the diaphragm and improved resting and exercise limb blood flow during inspiratory muscle loading as well as longer time to fatigue during handgrip exercise (14).

The finding of enhanced limb blood flow after IMT in this study provides a potential mechanism for an increase in aerobic performance after IMT in chronic HF patients. Prior studies in normal individuals by Dempsey et al. (15,16) have shown that the work of breathing incurred during maximal aerobic exercise causes vasoconstriction in leg muscles, compromising leg blood flow. This response, labeled the inspiratory muscle metaboreflex, seems to be mediated by the activation of type IV phrenic afferent fibers by accumulated metabolites, causing an increase in sympathetic outflow (17). The current study demonstrates that this reflex is exaggerated in chronic HF patients, further compromising limb blood flow, but that this adverse response is markedly attenuated by IMT (14). Limitations to the current study, appropriately acknowledged by the investigators, include the lack of a placebo IMT group, the 19-year greater mean age of the HF patients relative to control subjects, and the known hemodynamic differences between handgrip and aerobic exercise. Nevertheless, these researchers should be congratulated on extending their prior findings on the salutary effects of IMT in chronic HF patients.

The provocative findings of these 2 studies regarding the benefits of IMT in chronic HF (13,14) must be tempered by those of other investigators. Two prior randomized controlled trials of IMT failed to elicit improvement in exercise capacity or dyspnea in similar patient samples (18,19). In another study, the acute addition of respiratory dead space loading during cardiopulmonary exercise testing in patients with chronic HF did not reduce their peak VO₂, because the increased ventilatory requirement was met from their reserve capacity (20). Finally, acutely unloading the work of breathing by substituting helium for nitrogen in the inhaled gas mixture failed to increase peak treadmill VO₂, although exercise duration was lengthened (21). These negative studies are consistent with the diagnostic algorithm that separates cardiac from pulmonary causes of exertional dyspnea on the basis of a reduced ventilatory reserve capacity during peak exercise in pulmonary but not cardiac patients (22).

Given the conflicting findings in the published reports regarding the role of the lungs in limiting aerobic capacity in patients with chronic HF, what role should IMT have in this population? Clearly, a major issue requiring resolution is the proportion of chronic HF patients in whom inspiratory muscle weakness imposes a significant limitation to aerobic exercise. Although the experience of the Brazilian investigators featured in the current issue of the *Journal* suggests that approximately 30% of chronic HF patients have PImax <70% of predicted (14), the percentage of patients meeting this criterion likely varies substantially among centers. Of note, a small study by Hughes et al. (23) concluded that mild reduction of diaphragmatic strength occurs in chronic HF but overall respiratory muscle strength remains well preserved.

Several additional questions remain concerning the role of IMT in chronic HF. Can patients who are likely to benefit from IMT be identified clinically or should inspiratory muscle strength be determined in all HF patients? What are the optimal session frequency, intensity, and duration and the optimal program length for IMT? Are the benefits of IMT on exercise capacity and quality of life additive to those of conventional aerobic training programs? Perhaps most important, does IMT reduce the high morbidity and mortality of chronic HF? Indeed, the role of aerobic training remains unclear in this regard, although this ambiguity should be resolved with the completion of the multicenter National Institutes of Health (NIH)-sponsored HF-ACTION (Heart Failure and A Controlled Trial Investigating Outcomes of Exercise Training) trial within the next few months (24).

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