Exercise Training as Therapy for Heart Failure

Background

Despite a variety of pharmacological and device therapies for persons with chronic heart failure (HF), prognosis and quality of life (QOL) remain poor. The need for new effective strategies to improve outcomes for patients with HF is underscored by persistently high mortality, morbidity, healthcare use, and costs associated with HF, with >1 million US HF hospitalizations at an estimated direct and indirect cost in the US of $40 billion in 2012.1 Exercise intolerance is a primary symptom in patients with chronic HF, both those with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF), and is a strong determinant of prognosis and of reduced QOL.2 Exercise training improves exercise intolerance and QOL in patients with chronic stable HFrEF, and has become an accepted adjunct therapy for these patients (Class B level of evidence) based on a fairly extensive evidence base of randomized trials, mostly small.1

The National Heart, Lung, and Blood Institute–funded Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial compared an individualized, supervised, and home-based aerobic exercise program plus guideline-based pharmacological and device therapy with guideline-based therapy alone in persons with HFrEF. The exercise arm showed a modest reduction in cardiovascular hospitalizations and mortality and improved QOL.4,5 However, problems with adherence in the exercise arm probably dampened the potential benefit. This landmark study leaves several unanswered key questions, including the role of exercise dose; the relative benefit of different types of aerobic exercise, including high-intensity interval training (HIIT), and resistance, training relative to aerobic training; combination of exercise training with other therapies; optimization of adherence; benefit for older patients with HF, those with HFpEF or multiple comorbidities, and those with acute decompensated HF.

The National Heart, Lung, and Blood Institute convened a working group of experts on June 11, 2012 in Bethesda, MD to identify knowledge gaps and to suggest general approaches to filling those gaps for exercise training as a treatment for HF. The National Heart, Lung, and Blood Institute invited experts in a variety of areas, including basic and clinical exercise physiologists, HF and cardiac rehabilitation (CR) specialists, and clinical trial specialists to address these issues. Workshop participants were asked to identify knowledge gaps and to suggest general approaches in basic and clinical investigation to evaluate, to optimize, and to translate the potential role of exercise training in the treatment of HF.

They were asked to address the following specific questions:

1. What more needs to be learned about the pathophysiology of exercise intolerance in HFpEF and HFrEF to design better exercise treatments?
2. What do we need to learn about the mechanisms of exercise training, and of the training-related improvements (or lack thereof)?
3. What do we know about the need to tailor exercise regimens to specific HF population, for example, persons with multiple comorbidities, frail elderly, and women?
4. What evolving, innovative new exercise training modalities and combinations should be tested?
5. Can we begin rehabilitation earlier and in more severe, decompensated patients?
6. How can we improve long-term exercise adherence and maintenance?
7. How can we decrease the cost of exercise training interventions, whereas increasing their generalizability and dissemination (eg, home therapy, community centers, and avoidance of ECG monitoring)?
8. Is there a more efficient, yet clinically meaningful, outcome than mortality or exercise capacity in trials of HFP EF and HFREF?

Given the focus of this article on these questions, the reader is referred to excellent recent reviews of exercise training in HF for additional general information on this topic.6,7

Pathophysiology of Exercise Intolerance in HF: Cardiac Limitations
Exercise intolerance, typically quantified by the reduction in peak oxygen consumed during maximal effort exercise (peak VO₂), is a hallmark of HFP EF and HFREF.2 According to the Fick principle, VO₂ is equal to the product of cardiac output (CO) and arteriovenous oxygen difference (a-vO₂ diff). Thus, deficits in reserve capacity, that is, the change from rest to peak effort, in either component or both may cause reduction in peak VO₂ in HF. CO reserve limitation has been repeatedly shown to be not invariably observed in HFP EF and HFREF,4,5 and is related to impairments in both heart rate and stroke volume responses.6–10 An earlier study identified limited ability to recruit preload (left ventricular end-diastolic volume [LVEDV]) as the key mechanism limiting peak VO₂ in HFP EF,9 but a more recent study observed that EDV reserve is similar in HFP EF and controls.10 Chronotropic reserve is typically blunted in both HFREF and HFP EF,2,8–10 and it remains unknown whether EDV reserve would be similar if heart rate during exercise were higher in HFP EF, as with exercise pacing. Although EDV reserve is preserved in HFP EF, the increase in LV filling pressures required to achieve adequate EDV is much greater than what is observed in healthy controls.11 This elevation in LV filling pressures causes secondary elevation in pulmonary artery pressure which may affect right ventricular performance, and acute LV filling pressures elevation during exercise is thought to play the dominant role in promoting symptoms of exertional dyspnea, although the underlying mechanisms remain poorly understood. Limitation in stroke volume reserve in both HFREF and HFP EF is related to decreased ability to reduce LV end-systolic volume.5–11 There is an evidence that the latter finding is related to impairments in both contractile and vasodilatory reserve responses with exercise.

In HFREF exercise, training is generally associated with improved exercise CO and stroke volume, lower heart rate at submaximal workloads, reductions in resting LV volumes, and no changes in resting or exercise filling pressure or pulmonary artery pressures.12,13 Central effects of training in HFP EF have been minimal in the few studies to date.14,15

The pathophysiology of HFP EF in many ways represents an exaggeration of normal cardiovascular aging. Even healthy aging leads to cardiac stiffening16,17 that can be prevented by lifelong exercise training.17 Aging also leads to slowing of relaxation, a seemingly inevitable consequence of senescence that is not modified even by prolonged and intensive training.18 Patients with HFP EF seem to have hearts that are less distensible than those of sedentary, age-matched controls, with increased wall stress, slower relaxation, and impaired ventriculo-arterial coupling.19 These changes lead to markedly increased filling pressures during exercise, which likely contribute to dyspnea and exercise intolerance.20,21 This slowed cardiac relaxation may be compounded by abnormalities in skeletal muscle oxygen use, which augment the CO response to exercise, increasing flow into a small, stiff, and slowly relaxing heart.10,11

Although short-term exercise training studies in the healthy elderly22 or patients with HFP EF typically show significant improvements in functional capacity as estimated by VO₂ max, the mechanism of this improvement is uncertain. Evidence is strongest for improvements in oxygen extraction by skeletal muscle (a-vO₂ diff),14 with little evidence for altered cardiovascular structure even in long-term studies. For example, 1 year of training of sedentary seniors failed to improve ventricular compliance or estimated aortic age although it did increase VO₂ max and facilitate ventriculo-arterial coupling.24 Similarly, a full year of training in 12 invasively studied patients with HFP EF failed to alter cardiac compliance or improve ventriculo-arterial coupling.15 One potential mechanism for the apparent limited plasticity of cardiac training responses in patients with HFP EF may be the presence of advanced glycation end products, which increase with normal aging but are present to a greater degree in patients with HF and diabetes mellitus.25 Recent data in rats suggest that breaking these end products, combined with exercise training, may reverse the consequences of sedentary aging,26 although this must be confirmed in human studies.

Key Knowledge Gaps:

1. Are there overarching, systemic processes in HFP EF or HFREF that underlie the global impairments in cardiac and peripheral reserve that might be targeted therapeutically to improve overall exercise capacity and reduce morbidity/mortality?
2. Would approaches to phenotype the predominant mechanism(s) of exercise intolerance (central versus peripheral) in the individual patient improve understanding of pathophysiology and optimize treatment approaches in HFP EF or HFREF?
3. What is the optimal dose (frequency, duration, intensity) and modality of exercise training that will be most effective in HFP EF?
4. Are there pharmacological strategies that can be combined with exercise training in HFP EF to facilitate an improvement in cardiac and vascular compliance, blood flow delivery, or speed relaxation (cross-link breakers, nitrite donors, SERCA2a upregulators, and pericardial resection)?

Peripheral Mechanisms of Exercise Intolerance in HF
Substantial attention has focused on defining the central versus peripheral mechanisms underlying the reduced functional
capacity and symptoms among patients with HF as recently reviewed. To help redirect available blood flow and maintain arterial pressure during exercise in patients with HF, locomotory muscles experience enhanced sympathetic vasoconstriction, downregulation of endothelial vasodilatory function, and elevated venous pressures that impair the muscle pumping action to facilitate blood flow. Compelling evidence supports the concept that there may be a peripheral block in patients with HF that limits the ability to translate changes in central hemodynamics into changes in functional capacity, potentially accounting for the failure of many therapies to improve exercise tolerance, such as low LVEF, increased pulmonary wedge pressure, and other hemodynamic indices measured at rest do not predict exercise capacity in HF. Furthermore, intrinsic abnormalities are present in skeletal muscles of patients with HF compared with aerobically matched sedentary normal controls, resulting in anaerobic metabolism of patients with HF compared with aerobically matched sedentary normal controls. more, intrinsic abnormalities are present in skeletal muscles of patients with HF compared with aerobically matched sedentary normal controls, resulting in anaerobic metabolism (measured using 31P-MRI) in leg skeletal muscle of patients with HF, both under basal conditions and after occluding skeletal muscle blood flow. In addition, acute use of inotropes and vasodilators does not translate into increases in exercise tolerance or reduction of early anaerobic metabolism, despite improving leg blood flow and CO. Conversely, exercise training improves lactate threshold and aerobic capacity, but without significantly improving CO in both HFrEF and HFpEF. What is less clear is the temporal sequence of central and peripheral changes in HF, which has important implications for informing new therapeutic strategies. Figure 1 represents a model of how left ventricular systolic dysfunction, induced by a myocardial insult with decreased CO, can lead to impaired exercise tolerance and how exercise training may reverse such changes.

Figure 1. The figure presents a model of how left ventricular systolic dysfunction, induced by a myocardial insult with decreased cardiac output (CO), can lead to impaired exercise tolerance and how exercise training may reverse such changes. Pathophysiological responses at each step are represented in large type and the corresponding mechanisms are represented in small type in brackets. Potential points at which exercise training has been shown to induce a physiological response that might block progression to symptomatic exercise intolerance are shown with flat-headed arrows. Reprinted from Kraus et al with permission of the publisher. Copyright ©2010, Elsevier. ACE indicates angiotensin-converting enzyme; Ang II, angiotensin II; EC, electrochemical; NO, nitric oxide; and SKM, skeletal muscle.

Esposito et al have demonstrated that HF severely reduces muscle oxygen diffusion conductance (DO2m), helping to explain why increasing O2 delivery to skeletal muscle via vasodilators in HF might not yield expected increases in muscle O2 consumption during aerobic exercise (Figure 2). The impaired DO2m may also help to account for poor muscle function and exercise intolerance in both HFrEF and HFpEF. Determining the mechanistic bases for this reduced DO2m and developing strategies to correct it are crucial for increasing blood-muscle O2 flux in the face of limited O2 delivery, which may be relatively refractory to exercise training in many patients with HF.

Peripheral Mechanisms to Improve Exercise Tolerance With Training

In part, because of limitations in O2 delivery, patients with HF have an extremely slow increase of VO2 after the onset of acute exercise and also prolonged recovery. These slow kinetics create a greater perturbation of intramuscular high-energy phosphates (ie, Δ [creatine phosphate], [ADP free]) and pH, which exacerbate glycogenolysis and premature fatigue. Moreover, because these patients have a low lactate threshold, even at modest activity levels they incur the increased energetic costs associated with slow VO2 kinetics, which decreases muscle efficiency and raises the VO2 demands, thereby increasing the O2 deficit. Effectively improving blood-muscle O2 flux via exercise training has the potential to speed VO2 kinetics and reduce the VO2 requirement of exercise, that is, improved muscle efficiency. In addition, emerging evidence suggests that enhancing nitric oxide bioavailability by beetroot juice or inorganic nitrate supplementation can effectively lower the mitochondrial O2 cost of ATP production, thereby lowering the exercising VO2 requirement. Using these strategies, a therapeutic program that improves skeletal muscle O2 delivery, while simultaneously improving mitochondrial and contractile
efficiency might substantially improve metabolic function and exercise tolerance in patients with HF.

Key Knowledge Gaps:

1. Do pre-existing skeletal muscle characteristics determine responses to HF or is the converse true—skeletal muscle alterations are a consequence of the disease process?

2. Does exercise training ameliorate skeletal muscle alterations induced in HF? If so, do such salutary changes in skeletal muscle morphology predict improved clinical outcomes?

3. How quantitatively do events in the capillary decrease $\Delta O_2$ m in HF, are they similar in HFrdEF and HFPHF, and what are the most effective exercise training (duration, intensity, frequency: whole-body, small muscle mass) or alternative (nitric oxide, cytokines) strategies to reverse this pathophysiology?

4. Do exercise therapy–induced improvements in capillary hemodynamics (if they occur) effectively speed $O_2$ uptake kinetics and lower the $O_2$ cost of exercise?

**Effect of Aging, Frailty, and Comorbidities**

Aging per se is associated with a progressive decline in exercise capacity and decreased physiological reserve in cardiovascular function as well as in most other organ systems, altered pharmacological responses, increased adverse effects of medical therapy, and prolonged and often incomplete recovery. The prevalence and incidence of HF increase sharply after middle age. In the subset >80 years of age, ≤20% have prevalent HF, and the incidence of HF is rising fastest in this group. Approximately 88% of HF deaths and >75% of HF hospitalizations occur in patient’s aged >65 years. Despite these demographics, older persons are significantly under-represented in HF studies, especially those involving exercise training. In an analysis of 59 general HF trials conducted from 1985 to 1999 in >45,000 patients, the average age of participants was 61.4 years, whereas it is >77 years in the community. In the HF-ACTION trial, the largest trial of exercise training in HF, the mean age of participants was 59.5 years.

Outcomes of HF in the elderly have not changed substantially in the past 2 decades, despite advances in HF therapies. This may be because of the combined effect of multiple comorbidities and frailty. The majority of older patients have multiple comorbidities, and a high proportion are frail. The adverse effects of aging, frailty, and comorbidities on functional capacity and clinical outcomes are cumulative and synergistic. This synergy may be mediated in large part by the reduction in physical activity that accompanies each condition.

Perhaps the most prominent difference between in older versus younger patients with HF is the greater prevalence and severity of comorbidities in the former group. Common comorbidities in the elderly that further reduce exercise capacity and complicate therapy include diabetes mellitus, cerebrovascular and peripheral artery disease, musculoskeletal disorders, and renal, pulmonary, and cognitive dysfunction. It is noteworthy that patients with major or multiple comorbidities have often been actively excluded from clinical HF studies, thereby producing results that may not be applicable to typical older patients with HF, who typically have ≥5 comorbidities, many of which are noncardiac. Mounting evidence indicates that noncardiac comorbidities strongly contribute to adverse outcomes in patients with HF. Over 50% of subsequent events in recently hospitalized patients with HF are related to noncardiac comorbidities.

Frailty is highly prevalent in older patients with HF. Although there is an incomplete consensus on its specific definition, frailty is marked by excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event. It is manifested by slowness, weaknesses, perception of exhaustion, lower activity levels, and involuntary weight loss. Frailty contributes to worse clinical outcomes, which may be ameliorated by disease management programs. The effects of aging, multiple comorbidities, and frailty on the use of exercise training in older patients with HF are profound. The marked impairment of aerobic capacity, ambulatory function, strength, and balance often seen in this population presents major challenges to effectively and safely implement exercise training.

Key Knowledge Gaps:

1. What are the mechanisms whereby aging, noncardiac comorbidities, and frailty affect physical function outcomes in HF?

2. How can we develop and test novel exercise and physical function interventions that directly address the adverse effect of multiple comorbidities and frailty in older patients with HF.

**Sex Differences in HF and Their Implications for Therapy**

Several important sex differences in the clinical profile of patients with HF have been consistently observed. First, women with HF are generally about a decade older than men, and are, therefore, more likely to have multiple comorbidities and greater frailty. A noncoronary heart disease cause of HF is more common in women than men, which may explain, in part, their higher ejection fraction and thus a greater proportion with preserved LVEF. Conversely, diastolic dysfunction is more commonly observed cause for HF in women. Regardless of pathogenesis or the contribution of diastolic versus systolic dysfunction, women with HF generally have a lower functional capacity than men with comparable levels of clinical HF severity. The lower peak $V_O_2$ by New York Heart Association Class for women versus men reported by others was also observed in the HF-ACTION trial, the largest database of cardiopulmonary testing in women with HF although the sex gap narrowed as New York Heart Association Class worsened. These values of peak $V_O_2$ must be analyzed in the context of typical values for sedentary women of similar age. From a nomogram developed by Gulati et al for women without known heart disease, a typical 80-year-old woman has a predicted aerobic capacity of 4.3 METS (metabolic equivalents; 15.1 mL/kg per minute), which approximates that in younger, predominately male HF population, such as in HF-ACTION. The contribution of deconditioning and adaptation of skeletal muscle to the HF milieu may vary by sex, with men but not with women developing abnormalities
not attributable to deconditioning alone. Whether the mechanisms of exercise intolerance in women with HF differ from those in men is unresolved.

Although peak VO\(_2\) is strongly predictive of survival in both sexes, women show better survival for any given value. However, women with an ischemic versus nonischemic cause of HF seem to have a worse outcome for a given peak VO\(_2\), that is, especially prominent at lower values. Thus, HF cause may contribute strongly to prognosis in both the sexes. The HF-ACTION trial demonstrated a greater benefit of training in women than in men for the combined end points of all-cause mortality or all-cause hospitalization, primarily because of lower hospitalization rates, with no reduction in mortality. The mechanism for this differential benefit is unclear, but a significant interaction with pathogenesis was not observed, and both the sexes had similar adherence rates and achieved similar modest improvements in peak VO\(_2\) with training.

The contribution of hormonal status to exercise intolerance has not been systematically examined in women with HF. Estrogen levels decline with age and may be associated with endothelial dysfunction. Thus, the hormonal status of women with HF may contribute to their exercise intolerance. Although the overall concerns about estrogen replacement in older women have probably contributed to the paucity of work in this area, further studies of hormonal intervention in older women and men with HF are clearly needed. For example, testosterone supplementation has been shown in small studies to significantly improve exercise capacity and QOL in older women as well in older men with HF. Figure 3 is a model of the contributors to exercise intolerance in women versus men.

Key Knowledge Gaps:

1. How do the mechanisms of exercise intolerance in HF differ in women from men, and what role do sex hormone deficiencies play in these differences?

2. What, if any, fundamental differences in response to exercise training are seen in women with HF compared with that seen in men?

Beginning Rehabilitation Earlier and in More Severely Decompensated Patients

Physical impairments associated with chronic HF often worsen markedly with decompensation and can be further compounded by prolonged immobility associated with the hospital environment, creating profound impairments in physical function. For instance, 6-minute walk distance in patients hospitalized with HF is approximately half of that seen in chronic stable patients with HF. However, physical impairments are not limited to endurance. Most patients hospitalized with acute HF syndrome (AHFS) are frail elders with multiple comorbidities, including deficits in mobility, strength, and balance. Resulting functional impairments may persist or even progress after hospital discharge and are associated with an increased risk of adverse clinical outcomes, including rehospitalization and death. These findings suggest the potential for extending physical function interventions to patients hospitalized with AHFS.

Studies of exercise training in HF have focused almost exclusively on chronic, stable patients with HF. HF-ACTION, the largest study of exercise training in an HF population, specifically excluded patients with any clinical instability, including hospitalization, within 6 weeks of enrollment. This literature about the safety and efficacy of exercise interventions that specifically target patients with AHFS is limited to observational data and a small randomized trial, both of which showed benefit. A state-of-the-art review and the recent Center for Medicare and Medicaid Services coverage memo for CR in patients with chronic stable HF specifically exclude patients with AHFS or recent (4–6 weeks) hospitalization, and call for a period of stability before enrollment in CR. Furthermore,

Figure 3. Possible mechanisms of exercise intolerance in heart failure (HF) as related to sex. Areas that have been associated with women are in bold. The modifiers of the responses are in red and in italics. Thus, age may have a more profound effect on the exercise intolerance of women with HF and the level of fitness before disease onset. Estrogen as a modifier has been poorly studied in HF. HFpEF indicates HF with preserved ejection fraction; and HFrEF, HF with reduced ejection fraction.
traditional aerobic exercise training alone, the primary focus of previous HF exercise research, does not address the multidomain deficits present in this frail population, including muscle wasting, and impaired balance and flexibility. Initiating traditional exercise training without addressing these deficits and other special needs could cause injuries and worsen outcomes. Indeed, there are reports of increased adverse events, including injuries and falls, associated with standard rehabilitation interventions in frail older population.51,62

Given the severity and multidomain nature of their physical impairment, multiple comorbidities, and limited applicability of previous exercise training trials in chronic HF, additional research is needed to guide the development and implementation of rehabilitation programs specifically designed for older patients hospitalized with AHFS. Longitudinal studies are needed to fully define the physical function impairments in these patients and their trajectory of functional recovery novel rehabilitation interventions that address the specific needs of frail, older patients hospitalized with AHFS should be carefully developed and formally tested in clinical trials.

Key Knowledge Gaps:

1. What are the contributions of frailty, multiple comorbidities, cognitive deficits, and other factors to the functional impairments after hospitalization for AHFS?
2. Can exercise interventions during or immediately after hospitalization in frail older patients with AHFS, be implemented safely and improve key outcomes, such as physical function, QOL, and readmissions? If so, what is the optimal design for such interventions?

Traditional and Innovative Exercise Training Modalities in HF

Exercise intervention trials for clinically stable patients with HFpEF and HFrEF have primarily focused on continuous moderate-intensity aerobic training.4,5,8,61 Despite favorable antiremodeling and QOL benefits, moderate-intensity training is associated with only modest improvements in peak VO2,63,64 which averaged 3.0 mL/kg per minute in meta-analyses of both the patients with HFpEF65 and HFrEF.66 Accordingly, there has been recent interest in the role of HIIT on improving peak VO2 in individuals with clinically stable HF. Wisloff laboratory65 reported that HIIT, characterized by acute bouts of brief (4 minutes/bout) repeated vigorous near-maximal exercise (≥85% peak VO2) alternated with low-intensity recovery exercise, is superior to continuous moderate-intensity aerobic training for improving peak VO2, LVEF, and brachial artery flow-mediated dilation in clinically stable older patients with HFrEF. Fu et al66 extended these findings by demonstrating that 3 months of HIIT significantly increased peak VO2 secondary to enhanced peak exercise stroke volume and CO in older patients with HFrEF, with no significant change in A-VO2 diff. In contrast, Dimopoulos et al67 and Iellamo et al68 found that the increase in peak VO2 was similar after 3 months of continuous moderate-intensity versus HIIT exercise in patients with HFrEF. A meta-analysis of 7 small trials in patients with HFrEF showed that HIIT was more effective than traditional continuous moderate-intensity exercise in augmenting peak VO2 (difference of 2.1 mL/kg per minute), whereas increases in LVEF did not differ significantly.69 To date, the safety and efficacy of HIIT in patients with HFpEF has not been studied.

Traditionally, exercise training guidelines for patients with HF recommend large muscle mass (walking and cycling) aerobic exercise. However, in the setting of reduced convective O2 delivery as occurs in HF (Figure 2), whole body exercise may not be the most effective mode of training to increase peak VO2. Esposito et al16 demonstrated that 2 months of 1 leg knee extensor exercise resulted in a significant increase in leg and total body VO2 during cycle or knee extensor exercise, secondary to increased convective and diffusive O2 transport. Vastus lateralis fiber cross-sectional area, percent type I fibers, capillary to fiber ratio, number of capillaries surrounding a muscle fiber, and mitochondrial volume density were also significantly higher after training. Accordingly, localized muscle training may be an important type of training to improve convective and diffusive O2 transport in HF and could be particularly useful in severely disabled patients with minimal reserve capacity.

Key Knowledge Gaps:

1. What is the optimal training intensity (high-intensity aerobic interval versus moderate-intensity continuous exercise), mode (whole body versus small muscle mass training—resistance training), and duration of training (short-term: 2–3 months versus ≥1 year) to improve cardiovascular and skeletal muscle function, health status, physical functional performance, and survival in patients with HFrEF and HFpEF?

Exercise Training Combined With Other Treatment Strategies for Patients With Heart Failure

Because chronic patients with HF receive multiple cardiac medications and often device therapy or surgical interventions, it is important to assess the use of exercise training in combination with such background therapy. For example, a small crossover trial demonstrated additive effects of exercise training and lisinopril on exercise capacity in patients with moderate to severe systolic HF.70 Previous studies have shown that patients with HF receiving guideline-based β-blocker therapy exhibit training-induced increases in peak VO2 similar to those not receiving β-blockers.71,72

The ability of cardiac resynchronization therapy to improve peak VO2 has been shown in randomized controlled trials (RCTs). At least 2 studies have demonstrated additive effects of cardiac resynchronization therapy and exercise training on peak VO2 as well as hemodynamic indices and QOL.72,73 More recently, an 8-week program of aerobic and strength training improved peak VO2 by an average of 3.0 mL/kg per minute in patients with a left ventricular assist device as a bridge to transplantation.74 These encouraging findings require confirmation in larger trials, including the growing number of patients with HF receiving these devices as destination therapy. Finally, exercise training has been increasingly used in patients with HF after cardiac transplantation, in whose muscle wasting and exercise intolerance are common. A meta-analysis of 6 studies reported a significant 2.3 mL/kg per minute mean increase of
peak VO$_2$ and significant improvements in chest and leg press strength after exercise training in transplant recipients.\textsuperscript{75}

Most studies that focus on exercise training in patients with HF provide limited information about other interventions that patients may have received during the training. Although many of these studies take place in CR or other healthcare settings, it is likely that patients experienced opportunities to obtain further lifestyle education or to engage healthcare providers about a change in their symptoms. This additional access to healthcare providers in many ways mirrors disease-management interventions.\textsuperscript{76} In previous studies of older patients with HF, a CR program that included exercise training and additional patient education improved New York Heart Association status, QOL, 6-minute walk distance, reduced all-cause and cardiovascular hospitalizations, and days in the hospital.\textsuperscript{77,78} The benefit of participating in a multifaceted training program on exercise capacity, QOL, and HF hospitalizations has been shown to extend ≤10 years.\textsuperscript{79} However, addition of an exercise training program to a nurse-directed HF clinic and home visits that were received by both the exercise training and the usual care cohorts did not improve QOL or reduce clinical events, including mortality or hospitalization.\textsuperscript{80}

Knowledge Gaps:

1. What are the optimal strategies to complement, extend, and magnify the beneficial effects of exercise training in patients with HF?
2. Are there structured approaches to uniform reporting that could facilitate translation of interventions into patient care?

### Adherence Issues in Exercise Training

There are substantive potential health benefits of exercise for individuals with HF. However, the major clinical obstacle confronting the use of exercise training as a therapeutic option in the HF population is how to get individuals to initiate and maintain an exercise training program. This is illustrated by the experience of the HF-ACTION trial. Despite a well-organized and resourced effort to optimize adherence, only ≈40% of patients in the intervention arm achieved the target of 90 minutes of exercise per week at 3 months.\textsuperscript{4,5} Perhaps as a result, the mean increase in peak VO$_2$ was only 0.6 mL/kg per minute, potentially limiting the ability to evaluate the benefits of training on clinical outcomes fully. This experience is similar to that of some other exercise training trials in HF although better adherence was found in some smaller, single-center trials, as summarized in the Table.\textsuperscript{13,81-84} Adherence issues also played a major role in the conduct and evaluation of other major lifestyle intervention trials, including the Multiple Risk Factor Intervention Trial\textsuperscript{85} and the Diabetes Prevention Program.\textsuperscript{56}

Conventional wisdom suggests that adherence issues are primarily related to neurobehavioral and social issues, and barriers can be identified and addressed using behavioral approaches. Although most attention about adherence to lifestyle interventions has traditionally focused around psychosocial/behavioral factors, it is conceivable that biological factors may also help to determine whether individuals maintain an exercise program once initiated. There are studies of biological predictors of physical activity behavior, including genetic markers.\textsuperscript{32} If we are to maximize the salutary effects of regular exercise in individuals with HF, more information about the predictors of adherence to regular physical activity must be acquired, so as to identify individuals for whom more effective strategies to increase adherence can be applied. In addition, novel interventions to improve adherence are critically needed.

Key Knowledge Gaps:

1. What are the predictors of adherence to exercise in chronic patients with HF, beyond what can be currently identified?
2. What interventions optimize adherence to exercise in chronic patients with HF?

### How Can We Reduce Costs and Increase Use of Exercise Training in Patients with Heart Failure?

Despite the demonstrated benefits of exercise training in patients with HF, widespread implementation of formal CR and home-based training in this population presents special challenges. Patients with HF are often older, more deconditioned, and have more comorbidities than the typical coronary patient. Clinicians may be concerned about asking patients with HF to increase their activity because of fears of worsening ventricular function and symptoms. Many physicians lack awareness of the physiological benefits of exercise training, its safety and its potential to improve health status, and QOL in patients with HF. Lack of financial coverage has been another

### Table. Adherence of Heart Failure Patients to Exercise Training in Some Previous Trials

<table>
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<tr>
<th>Trial</th>
<th>Adherence Methodology</th>
<th>Adherence Findings</th>
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<tr>
<td>HF-ACTION\textsuperscript{4,5}</td>
<td>Follow-up phone calls and Physical Activity Questionnaire</td>
<td>40% performing exercise training as prescribed at month 3</td>
</tr>
<tr>
<td>Coats et al\textsuperscript{13}</td>
<td>Percentage of expected bicycle wheel revolutions</td>
<td>Mean adherence 77.3% (range 26%–116%)</td>
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<tr>
<td>Evangelista et al\textsuperscript{81}</td>
<td>Pedometers (10% improvement in scores)</td>
<td>20/38 (53%) patients found to be adherent</td>
</tr>
<tr>
<td>Corvera-Tindel et al\textsuperscript{82}</td>
<td>Pedometers (actual walking time/prescribed time)</td>
<td>Mean adherence 74.3±37% (n=42 in exercise training arm)</td>
</tr>
<tr>
<td>McKelvie et al\textsuperscript{83}</td>
<td>Prerandomization screening</td>
<td>43% attended ≥80% of sessions, 16% attended &lt;50% of sessions. Patients exercised 2.3±0.4 sessions/wk during the first month and 1.7±0.4 sessions/wk by month 12.</td>
</tr>
<tr>
<td>Oka et al\textsuperscript{84}</td>
<td>Activity logs and telephone contact</td>
<td>Average adherence 110% for aerobic, 87% for upper body, and 75% for lower body</td>
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HF-ACTION indicates Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training.
major deterrent to CR referral. In addition, primary care providers are typically unfamiliar with exercise prescriptions or how to derive them. Although the vast majority of patients with HF are in primary care practices, educating these physicians about the benefits and basics of exercise training in HF is a high priority.

In February 2014, the Center for Medicare and Medicaid Services approved coverage for CR for selected patients with chronic HF. The criteria match the HF-ACTION inclusion criteria, with stable medications for ≥6 weeks and LVEF ≤35%. This generally excludes patients with recent hospitalization and those with HFrEF. The dearth of supportive data in this latter group should be priorities for future studies. This important extension of CR coverage should facilitate CR use in chronic patients with HFrEF. Although private insurers and Medicaid traditionally follow Center for Medicare and Medicaid Services policy, CR may remain inaccessible for uninsured patients. Although cardiac monitoring was not required in the chronic patients with HF enrolled in HF-ACTION, costs could potentially be lower than for conventional CR. Future studies should address the feasibility and safety of offering community-based CR programs, potentially at YMCA’s, community centers, and churches.

Equipment for CR in patients with HF can be simple and relatively inexpensive. Walking programs require only appropriate footwear and a safe place to walk. Although home-based training programs are financially attractive, they introduce additional nonadherence issues. The greatest challenge facing the widespread use of CR is clinician education to overcome the current gap in evidence-based care, as illustrated by the low referral rates of coronary patients to traditional CR programs, despite ≥2 decades of favorable published outcome data. Convincing clinicians about the benefits of CR in patients with HF will probably be more difficult because of concerns of worsening LV function with exercise. Although patients respect the advice of their physicians, the latter should emphasize the importance of physical activity and CR for their patients with HF.

Key Knowledge Gaps:

1. How can we optimize physician adherence to CR and exercise therapy guidelines for patients with HF?
2. Can we develop cost-effective models of CR in patients with HF, including CR initiated early after hospitalization for AHFS?

Is There a More Efficient, Yet Clinically Meaningful Outcome Than Mortality or Exercise Capacity in HF Trials?

The RCT is the “gold standard” for evaluating the efficacy and safety of a therapeutic intervention. In designing and conducting an RCT, the balance between resources available and obtaining a reliable answer to the primary hypothesis generally requires making many compromises. Undoubtedly, the most critical decisions about the design of an RCT are the selection of the patient population and the determination of the primary end point. Both the estimated effectiveness of the intervention and the number of end point events are key factors in the sample size calculations.

In early RCTs of patients with HFrEF, all-cause mortality was frequently the primary outcome. The beneficial results on this, the most definitive of clinical end points, in several well done RCTs evaluating angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone receptor antagonists were impressive, convincing, and practice changing. In these RCTs, the benefits of the tested therapies on deaths attributed to cardiovascular causes had to be so pronounced that robust statistical significance could be demonstrated, despite the presumption that the therapy would not have a positive effect on rates of noncardiovascular deaths, such as cancer, trauma, infectious, and other causes.

As mortality rates for cardiovascular disease, including HF, have declined overtime, all-cause mortality, the undisputed heavyweight champion of RCT end points, is not a viable option for most RCTs of typical HF population. In addition, the lower absolute mortality and the higher proportion of noncardiovascular modes of death in patients with HFrEF versus HFrEF render all-cause mortality, an impractical and nonspecific primary outcome in RCTs of patients with HFrEF.

Composite outcomes combining nonfatal and fatal outcomes have been frequently adopted. In a cohort selected for symptomatic HF, combining cardiovascular death with nonfatal hospitalization for HF is a frequent and reasonable primary target for therapeutic interventions. Using a cause-specific clinical outcome as the primary objective of RCTs would be anticipated to be more sensitive to the effects of a targeted intervention, resulting in a lower sample size. Of course, data on all-cause mortality and other serious nonfatal events must still be collected and presented as supporting efficacy and safety information. The interpretation of composite outcome results can be straightforward when there is a congruence of the effect of the intervention on all components of the composite outcome, but is more complicated when there is a discordance between the effects of the therapy on fatal and nonfatal events.

Other important goals of therapy, such as improving symptomatology, QOL as perceived by the patient using validated instruments, and exercise capacity are all acknowledged as clinically meaningful. The sample size required for an RCT powered for these outcomes, ascertained at multiple times in all enrolled patients, is generally much lower than in RCTs with a primary end point of major morbidity and mortality. Similarly, pilot interventions probing whether biomarkers associated with adverse outcomes, such as brain natriuretic peptides, are altered by therapy can also be conducted with a smaller patient sample. However, it must be acknowledged that these smaller trials using surrogate end points cannot provide a reliable estimate of either the effect on clinical outcomes or the safety of the therapeutic intervention being evaluated. Figure 4 represents a theoretical hierarchy of possible RCT outcomes and their relationship to the sample size required.

Key Knowledge Gaps:

1. What outcomes, including novel patient-centered composite outcomes, best capture the relative effectiveness of exercise interventions in patients with HF, and when are surrogate outcomes appropriate?
Working Group Recommendations

The Working Group participants voted the following recommendations as the highest priority in advancing exercise training as a therapy for patients with HF:

1. Better elucidate the basic mechanisms of impaired cardiac, vascular, and peripheral muscle function and the effect of exercise training on them. Examples might include determining the mechanistic basis for the decreased muscle oxygen diffusing capacity in HF and the effect of exercise training in reversing it.

2. Better phenotype the predominant mechanism of exercise intolerance in individual patients to optimize exercise training approaches. Clarify differences between patients with HFrEF versus HFpEF; effects of obesity, sarcopenia, chronotropic incompetence, impaired peripheral vascular responses, etc.

3. Determine the best measures to assess and to quantify exercise intolerance in patients with HF and their responses to exercise training. Potential candidates include peak VO$_2$, ventilatory threshold, other ventilatory variables, critical power, treadmill time/estimated METS, and 6-minute walk distance.

4. Develop interventions to improve adherence to exercise training programs/regimens. Examples include better defining causes of nonadherence and developing educational and motivational tools, user-engaging and personalized training programs.

5. Optimize exercise training regimens through better tailoring to different types of patients. Variables to consider include exercise mode, program duration, frequency, and intensity, and use of novel training techniques (high-intensity intervals, prolonged sessions, optimal mix of aerobic, resistance, balance, and flexibility). Patient variables to consider include age, sex, comorbidities, frailty, and socioeconomic factors. Other variables include the potential safety and efficacy of beginning training early after acute decompensated HF or even during hospitalization.

6. Test combinations of exercise training with other lifestyle interventions, drugs, and devices. Examples might include formal CR, caloric and sodium restriction, new drugs, cardiac resynchronization therapy, and conventional cardiac pacing.

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