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Exercise Training as Therapy for Heart Failure: Current Status and Future Directions

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Background

Despite a variety of pharmacologic and device therapies for persons with chronic heart failure (HF), prognosis and quality of life (QOL) remain poor. The need for new effective

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strategies to improve outcomes for patients with HF is underscored by persistently high mortality, morbidity, health care utilization and costs associated with HF, with over 1.million U.S. HF hospitalizations at an estimated direct and indirect cost in the U.S. of $ 40 billion in 2012. (1)

Exercise intolerance is a primary symptom in chronic HF patients, 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 (ET) 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. (3)

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

The NHLBI convened a working group of experts on June 11, 2012 in Bethesda, Maryland to identify knowledge gaps and to suggest general approaches to filling those gaps for exercise training as a treatment for HF. The NHLBI invited experts in a variety of areas, including basic and clinical exercise physiologists, HF and cardiac rehabilitation 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, optimize, and 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 in order to design better exercise treatments?
2. What do we need to learn regarding 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 populations, e.g., 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, while increasing their generalizability and dissemination (e.g., home therapy, community centers, avoidance of ECG monitoring)?

8. Is there a more efficient, yet clinically meaningful, outcome than mortality or exercise capacity in trials of HFpEF and HFrEF?

Given the focus of the current manuscript 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 Heart Failure: Cardiac Limitations

Exercise intolerance, typically quantified by the reduction in peak oxygen consumed during maximal effort exercise (peak VO_2), is a hallmark of HFpEF and HFrEF. (2) According to the Fick principle, VO_2 is equal to the product of cardiac output (CO) and arteriovenous oxygen difference (a-vO_2 diff).Thus, deficits in reserve capacity, i.e., the change from rest to peak effort, in either component or both may cause reduction in peak VO_2 in HF. CO reserve limitation has been repeatedly though not invariably observed in HFpEF and HFrEF, and is related to impairments in both heart rate (HR) and stroke volume (SV) responses. (6–10) An early study identified limited ability to recruit preload (LV end diastolic volume, EDV) as the key mechanism limiting peak VO_2 in HFpEF (9), but a more recent study observed that EDV reserve is similar in HFpEF and controls (10). Chronotropic reserve is typically blunted in both HFrEF and HFpEF (2,8–10), and it remains unknown whether EDV reserve would be similar if HR during exercise were higher in HFpEF, as with rate-adaptive pacing. Though EDV reserve is preserved in HFpEF, the increase in LV filling pressures (LVFP) required to achieve adequate EDV is much greater than what is observed in healthy controls. (11) This elevation in LVFP causes secondary elevation in pulmonary artery pressure which may affect right ventricular performance, and acute LVFP elevation during exercise is believed to play the dominant role in promoting symptoms of exertional dyspnea, though the underlying mechanisms remain poorly understood. Limitation in SV reserve in both HFrEF and HFpEF is related to decreased ability to reduce LV end systolic volume. (8–11) There is 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 cardiac output 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 HFpEF have been minimal in the few studies to date. (14,15)

The pathophysiology of HFpEF in many ways represents an exaggeration of “normal” cardiovascular aging. Even healthy aging leads to cardiac stiffening(16,17) 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 HFpEF appear 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 leads to markedly increased filling pressures during exercise which likely contributes to dyspnea and exercise intolerance.(20,21) This slowed cardiac relaxation may be compounded by abnormalities in skeletal muscle oxygen utilization which augment the CO response to exercise, increasing flow into a small, stiff, slowly relaxing heart. (10,11)

Although short-term exercise training studies in the healthy elderly (22) or patients with HFpEF (23) typically show significant improvements in functional capacity as estimated by VO_2max, the mechanism of this improvement is uncertain. Evidence is strongest for improvements in oxygen extraction by skeletal muscle (a-vO_2 diff) (14), with little evidence for altered CV structure even in long-term studies. For example, one year of training of sedentary seniors failed to improve ventricular compliance or estimated aortic age although it did increase VO_2max and facilitate ventriculo-arterial coupling. (24) Similarly, a full year of training in 12 invasively studied HFpEF patients failed to alter cardiac compliance or improve ventricular-arterial coupling. (15) One potential mechanism for the apparent limited plasticity of cardiac training responses in HFpEF patients 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. (25) Recent data in rats suggests that breaking these end-products, combined with exercise training, may reverse the consequences of sedentary aging (26), though this must be confirmed in human studies.

Key Knowledge Gaps:

1. Are there overarching, systemic processes in HFpEF 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 HFpEF or HFrEF?
3. What is the optimal “dose” (frequency, duration, intensity) and modality of exercise training that will be most effective in HFpEF?
4. Are there pharmacologic strategies that can be combined with exercise training in HFpEF to facilitate an improvement in cardiac and vascular compliance, blood flow delivery, or speed relaxation (cross-link breakers, nitrite donors, SERCA2a up-regulators, pericardial resection)?

Peripheral Mechanisms of Exercise Intolerance in Heart Failure

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. (27) To help redirect available blood flow and maintain arterial pressure during exercise in HF patients, locomotory muscles experience enhanced sympathetic vasoconstriction, down regulation 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 HF patients 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: Low LVEF, increased pulmonary wedge pressure, and other hemodynamic indices measured at rest do not predict exercise capacity in HF. (28,29) Furthermore, intrinsic abnormalities are present in skeletal muscles of HF patients compared to aerobically matched sedentary normal controls (30,31), resulting in anaerobic metabolism (measured using 31P–MRI) in leg skeletal muscle of HF patients, both under basal conditions and after occluding skeletal muscle blood flow. (32,33) 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. (34,35) Conversely, exercise training improves lactate threshold and aerobic capacity, but without significantly improving CO in both HFrEF (12) and HFpEF . (14) 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 presents 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.

Esposito and colleagues (36) have demonstrated that HF severely reduces muscle oxygen diffusion conductance (DO_2m), helping to explain why increasing O_2 delivery to skeletal muscle via vasodilators in HF might not yield expected increases in muscle O_2 consumption during aerobic exercise (Figure 2). The impaired DO_2m may also help account for poor muscle function and exercise intolerance in both HFrEF and HFpEF. (37) Determining the mechanistic bases for this reduced DO_2m and developing strategies to correct it are crucial for increasing blood-muscle O_2 flux in the face of limited O_2 delivery, which may be relatively refractory to exercise training in many HF patients.

Peripheral Mechanisms to Improve Exercise Tolerance with Training

In part because of limitations in O_2 delivery, HF patients have an extremely slow increase of VO_2 following the onset of acute exercise and also prolonged recovery. (38) These slow kinetics create a greater perturbation of intramuscular high-energy phosphates (i.e., Δ [creatine phosphate], $[ADP_{free}]$) and pH, which exacerbate glycogenolysis and premature fatigue. (37,38) Moreover, because these patients have a low lactate threshold, even at very modest activity levels they incur the increased energetic costs associated with slow VO_2 kinetics , which decreases muscle efficiency and raises the VO_2 demands, thereby increasing the O_2 deficit. (37) Effectively improving blood-muscle O_2 flux via exercise training has the potential to speed VO_2 kinetics and reduce the VO_2 requirement of exercise, i.e., 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 O_2 cost of ATP production, thereby lowering the exercising VO_2 requirement. (39) Using these strategies, a therapeutic program that improves skeletal muscle O_2 delivery while simultaneously improving mitochondrial and contractile efficiency might substantially improve metabolic function and exercise tolerance in HF patients.

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 DO2m in HF, are they similar in HFrEF and HFPpEF, and what are the most effective exercise training (duration, intensity, frequency: whole-body, small muscle mass) and/or alternative (↑nitric oxide , ↓cytokines) strategies to reverse this pathophysiology?
4. Do exercise therapy-induced improvements in capillary hemodynamics (if they occur) effectively speed O2 uptake kinetics and lower the O2 cost of exercise?

Impact 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. (1) In the subset over age 80 years, up to 20% have prevalent HF, and the incidence of HF is rising fastest in this group. Approximately 88% of HF deaths and over 75% of HF hospitalizations occur in person's age ≥ 65 years. (40) Despite these demographics, older persons are significantly under-represented in HF studies, especially those involving exercise training. (41,42) In an analysis of 59 general HF trials conducted from 1985–1999 in > 45,000 patients, the average age of participants was 61.4 years, whereas it is >77 years in the community. (42) In the HF-ACTION trial, the largest trial of exercise training in HF, the mean age of participants was 59.5 years. (4)

Outcomes of HF in the elderly have not changed substantially in the past 2 decades despite advances in HF therapies. (43) This may be due to the combined impact of multiple comorbidities and frailty. The majority of older patients have multiple comorbidities, and a high proportion are frail. The adverse impacts of aging, frailty, and comorbidities on functional capacity and clinical outcomes are cumulative and synergistic. (43) 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 HF patients 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, 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 HF patients, who typically have 5 or more comorbidities, many of which are non-cardiac. (44) Mounting evidence indicates

that non-cardiac comorbidities strongly contribute to adverse outcomes in HF patients. Over 50% of subsequent events in recently hospitalized HF patients are related to non-cardiac comorbidities. (45)

Frailty is highly prevalent in older HF patients. (43) Although there is 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, weakness, perception of exhaustion, lower activity levels, and involuntary weight loss. (46) 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 HF patients 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, non-cardiac comorbidities, and frailty impact physical function outcomes in HF.
2. How can we develop and test novel exercise and physical function interventions that directly address the adverse impact of multiple co-morbidities and frailty in older patients with HF.

Gender Differences in Heart Failure and Their Implications for Therapy

Several important gender differences in the clinical profile of HF patients 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. (47) A non-coronary heart disease etiology 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. (48) Conversely, diastolic dysfunction is a more commonly observed etiology for HF in women. Regardless of etiology 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. (49,50) The lower peak VO_2 by NYHA 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 gender gap narrowed as NYHA Class worsened. (50) These values of peak VO_2 must be analyzed in the context of typical values for sedentary women of similar age. From a nomogram developed by Gulati et al (51) for women without known heart disease, a typical 80-year old woman has a predicted aerobic capacity of 4.3 METS (15.1 ml/kg/min), which approximates that in younger, predominately male HF populations such as in HF-ACTION. (4,5) The contribution of deconditioning and adaptation of skeletal muscle to the HF milieu may vary by gender, with men but not women developing abnormalities not attributable to deconditioning alone. (30) 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. (49) However, women with an ischemic versus non-ischemic

etiology of HF appear to have a worse outcome for a given peak VO_2 that is especially prominent at lower values. (49) Thus, HF etiology may contribute strongly to prognosis in both sexes. The HF-ACTION trial demonstrated a greater benefit of training in women than men for the combined endpoints of all-cause mortality or all cause hospitalization, primarily due to lower hospitalization rates, with no reduction in mortality. (52) The mechanism for this differential benefit is unclear, but a significant interaction with etiology was not observed, and both sexes had similar adherence rates and achieved similar modest improvements in peak VO_2 with training. (52)

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 older men with HF. (53) 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 to 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. (54) For instance, six minute walk distance in patients hospitalized with HF is approximately half of that seen in chronic stable HF patients. (2,4,55,56) 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. (43,54) Resulting functional impairments may persist or even progress after hospital discharge (57) and are associated with an increased risk of adverse clinical outcomes, including re-hospitalization and death. (55–57) 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 HF patients. (58) HF-ACTION, the largest study of exercise training in a HF population, specifically excluded patients with any clinical instability, including hospitalization, within 6 weeks of enrollment. (4) The current literature regarding the safety and efficacy of exercise interventions that specifically target patients with AHFS is limited to observational

data (59) and a small randomized trial (60), both of which showed benefit. A state-of-the-art review (7) and the recent Center for Medicare and Medicaid Services (CMS) coverage memo for cardiac rehabilitation (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 prior to enrollment in CR. Furthermore, traditional aerobic exercise training alone, the primary focus of prior HF exercise research, does not address the multi-domain 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 populations (61,62).

Given the severity and multi-domain nature of their physical impairment, multiple comorbidities, and limited applicability of prior 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 Heart Failure

Exercise intervention trials for clinically stable patients with HFpEF and HFrEF have primarily focused on continuous moderate-intensity aerobic training. (4,58,63) Despite favorable anti-remodeling and QOL benefits, moderate-intensity training is associated with only modest improvements in peak VO_2. (63,64), which averaged 3.0 ml/kg/min in meta-analyses of both HFrEF (63) and HFpEF (64) patients. Accordingly, there has been recent interest in the role of high intensity interval training (HIIT) on improving peak VO_2 in individuals with clinically stable HF. Wisloff's laboratory (65) reported that HIIT, characterized by acute bouts of brief (4 minutes per bout) repeated vigorous near-maximal exercise (≥85% peak VO_2) alternated with lower-intensity recovery exercise, is superior to continuous moderate-intensity aerobic training for improving peak VO_2, LVEF, and brachial artery flow-mediated dilation in clinically stable older HFrEF patients. Fu et al. (66) extended these findings by demonstrating that 3 months of HIIT significantly increased peak VO_2 secondary to enhanced peak exercise SV and CO in older HFrEF patients, with no significant change in A-VO_2 diff. In contrast, Dimopoulos et al(67) and Iellamo et al (68)

found that the increase in peak VO_2 was similar after 3 months of continuous moderate-intensity versus HIIT exercise in HFrEF patients. 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 VO_2 (difference of 2.1 ml/kg/min) whereas increases in LVEF did not differ significantly.(69) To date, the safety and efficacy of HIIT in HFpEF patients has not been studied.

Traditionally, exercise training guidelines for HF patients recommend large muscle mass (walking, cycling) aerobic exercise. However, in the setting of reduced convective O_2 delivery as occurs in HF (Figure 2), whole body exercise may not be the most effective mode of training to increase peak VO_2. Esposito et al.(36) demonstrated that 2 months of one leg knee extensor exercise resulted in a significant increase in leg and total body VO_2 during cycle or knee extensor exercise, secondary to increased convective and diffusive O_2 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 O_2 transport in HF and could be particularly useful in severely disabled patients with minimal reserve capacity.

Key Knowledge Gaps:

1. 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 one year or longer) to improve cardiovascular and skeletal muscle function, health status, physical functional performance and survival in HFrEF and HFpEF patients?

Exercise Training Combined with Other Treatment Strategies for Heart Failure Patients

Because chronic HF patients receive multiple cardiac medications and often device therapy or surgical interventions, it is important to assess the utility 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) Prior studies have shown that HF patients receiving guideline-based beta blocker therapy exhibit training-induced increases in peak VO_2 similar to those not receiving beta blockers. (3,71)

The ability of cardiac resynchronization therapy to improve peak VO_2 has been shown in randomized controlled trials (RCTs). At least two 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 VO_2 by an average of 3.0 ml/kg/min 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 HF patients receiving

these devices as destination therapy. Finally, exercise training has been increasingly employed in HF patients after cardiac transplantation, in who muscle wasting and exercise intolerance are common. A meta-analysis of 6 studies reported a significant 2.3 ml/kg/min mean increase of peak VO2 and significant improvements in chest and leg press strength after exercise training in transplant recipients. (75)

Most studies that focus on exercise training in HF patients provide limited information regarding other interventions that patients may have received during the training. Since 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 regarding a change in their symptoms. This additional access to healthcare providers in many ways mirrors disease-management interventions. (76) In prior studies of older HF patients, a CR program that included exercise training and additional patient education improved NYHA status, QOL, six minute walk distance and reduced all-cause and CV hospitalizations and days in the hospital. (77,78) The benefit of participating in a multifaceted training program on exercise capacity, QOL, and HF hospitalizations has been shown to extend up to 10 years. (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. (80)

Knowledge Gaps:

1. What are the optimal strategies to complement, extend, and magnify the beneficial effects of exercise training in HF patients?
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/week at 3 months.(4,5) Perhaps as a result, the mean increase in peak VO_2 was only 0.6 ml/kg/min., potentially limiting the ability to fully evaluate the benefits of training on clinical outcomes. This experience is similar to that of some other exercise training trials in HF though better adherence was found in some smaller, single center trials, as summarized in the Table. (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 (85) and the Diabetes Prevention Program. (86) 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 regarding adherence to lifestyle interventions has traditionally focused around psychosocial/behavioral

factors, it is conceivable that biological factors may also help determine whether individuals maintain an exercise program once initiated. There are studies of biological predictors of physical activity behavior, including genetic markers. (87) If we are to maximize the salutary effects of regular exercise in individuals with heart failure, 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 HF patients, beyond what can currently be identified?
2. What interventions optimize adherence to exercise in chronic HF patients?

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

Despite the demonstrated benefits of exercise training in HF patients, widespread implementation of formal CR and home-based training in this population presents special challenges. HF patients are often older; more deconditioned, and have more comorbidities than the typical coronary patient. Clinicians may be concerned about asking HF patients to increase their activity, due to fears of worsening ventricular function and symptoms. Many physicians lack awareness of the physiologic 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 major deterrent to CR referral. In addition, primary care providers are typically unfamiliar with exercise prescriptions or how to derive them. Since the vast majority of HF patients 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 CMS approved coverage for CR for selected patients with chronic HF. The criteria match the HF-ACTION inclusion criteria, with stable medications for at least 6 weeks and LVEF ≤35%. This generally excludes patients with recent hospitalization as well as those with HFpEF. The dearth of supportive data in this latter group should be priorities for future studies. This important extension of CR coverage should facilitate CR utilization in chronic HFrEF patients. Although private insurers and Medicaid traditionally follow CMS policy, CR may remain inaccessible for uninsured patients. Since cardiac monitoring was not required in the chronic HF patients 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 HF patients 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 non-adherence 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 over 2 decades of favorable published outcome data. (88) Convincing clinicians about the benefits of CR in HF patients will likely be more difficult due to concerns of worsening LV function with exercise. Since patients respect the advice of their physicians, the latter should emphasize the importance of physical activity and CR for their HF patients.

Key Knowledge Gaps

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

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

The RCT is the “gold standard” for evaluating the efficacy and safety of a therapeutic intervention. In designing and conducting a 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 concerning design of a RCT are the selection of the patient population and the determination of the primary endpoint. Both the estimated effectiveness of the intervention and the numbers of endpoint 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 endpoints, in several well done RCTs evaluating ACE inhibitors, beta blockers and aldosterone receptor antagonists were impressive, convincing, and practice changing. In these RCTs the benefits of the tested therapies on deaths attributed to CV causes had to be so pronounced that robust statistical significance could be demonstrated despite the presumption that the therapy would not have a positive impact on rates of non-CV deaths such as cancer, trauma, infectious and other etiologies.

As mortality rates for CV disease, including HF, have declined over time, all-cause mortality, the undisputed heavyweight champion of RCT endpoints, is not a viable option for most RCTs of typical HF populations. In addition, the lower absolute mortality and the higher proportion of non-CV modes of death in patients with HFpEF versus HFrEF render all-cause mortality an impractical and nonspecific primary outcome in RCTs of HFpEF patients. (89)

Composite outcomes combining nonfatal and fatal outcomes have been frequently adopted. In a cohort selected for symptomatic HF, combining CV death with nonfatal hospitalization for HF is a frequent and reasonable primary target for therapeutic interventions. (90) 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. (91) 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 congruence of the effect of the intervention on all components of the composite outcome, but is more complicated when there is discordance between the effects of the therapy on fatal and nonfatal events. (92)

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 a RCT powered for these outcomes, ascertained at multiple times in all enrolled patients, is generally much lower than in RCTs with a primary endpoint 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 endpoints 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 HF patients, 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 HF patients:

1. Better elucidate the basic mechanisms of impaired cardiac, vascular, and peripheral muscle function and the impact 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 vs. HFpEF; effects of obesity, sarcopenia, chronotropic incompetence, impaired peripheral vascular responses, etc.
3. Determine the best measures to assess and quantify exercise intolerance in HF patients and their responses to exercise training. Potential candidates include peak VO2, ventilatory threshold, other ventilatory variables, critical power, treadmill time/estimated METS, 6-minute walk distance.
4. Develop interventions to improve adherence to exercise training programs/ regimens. Examples include better defining causes of non-adherence 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, flexibility). Patient variables to consider include age, gender, comorbidities, frailty, and socioeconomic factors. Other variables include the potential safety and efficacy of beginning training early after acute decompensated heart failure 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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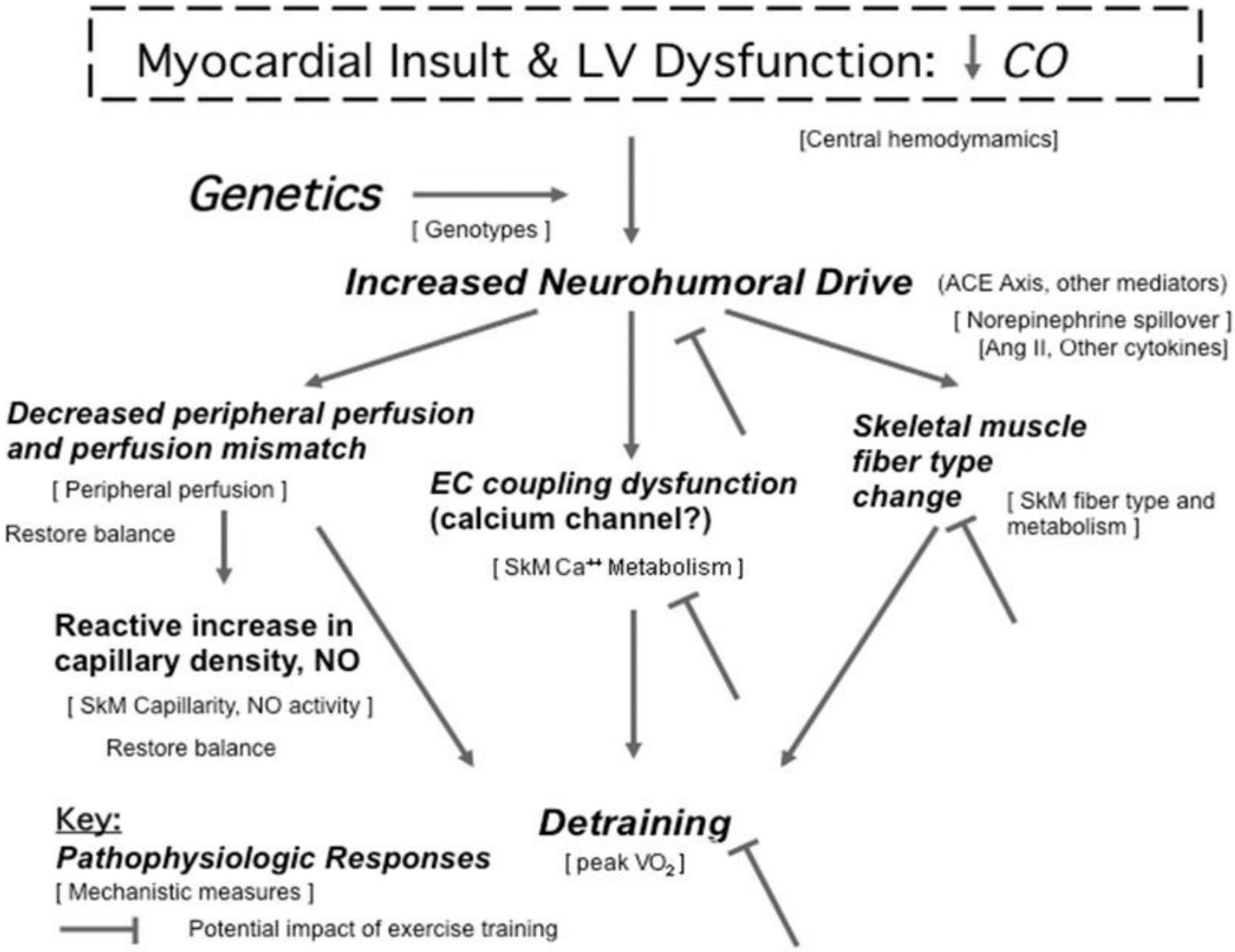

Figure 1.

The figure presents 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. Pathophysiologic 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 physiologic response that might block progression to symptomatic exercise intolerance are shown with flat headed arrows. Adapted from reference 27.

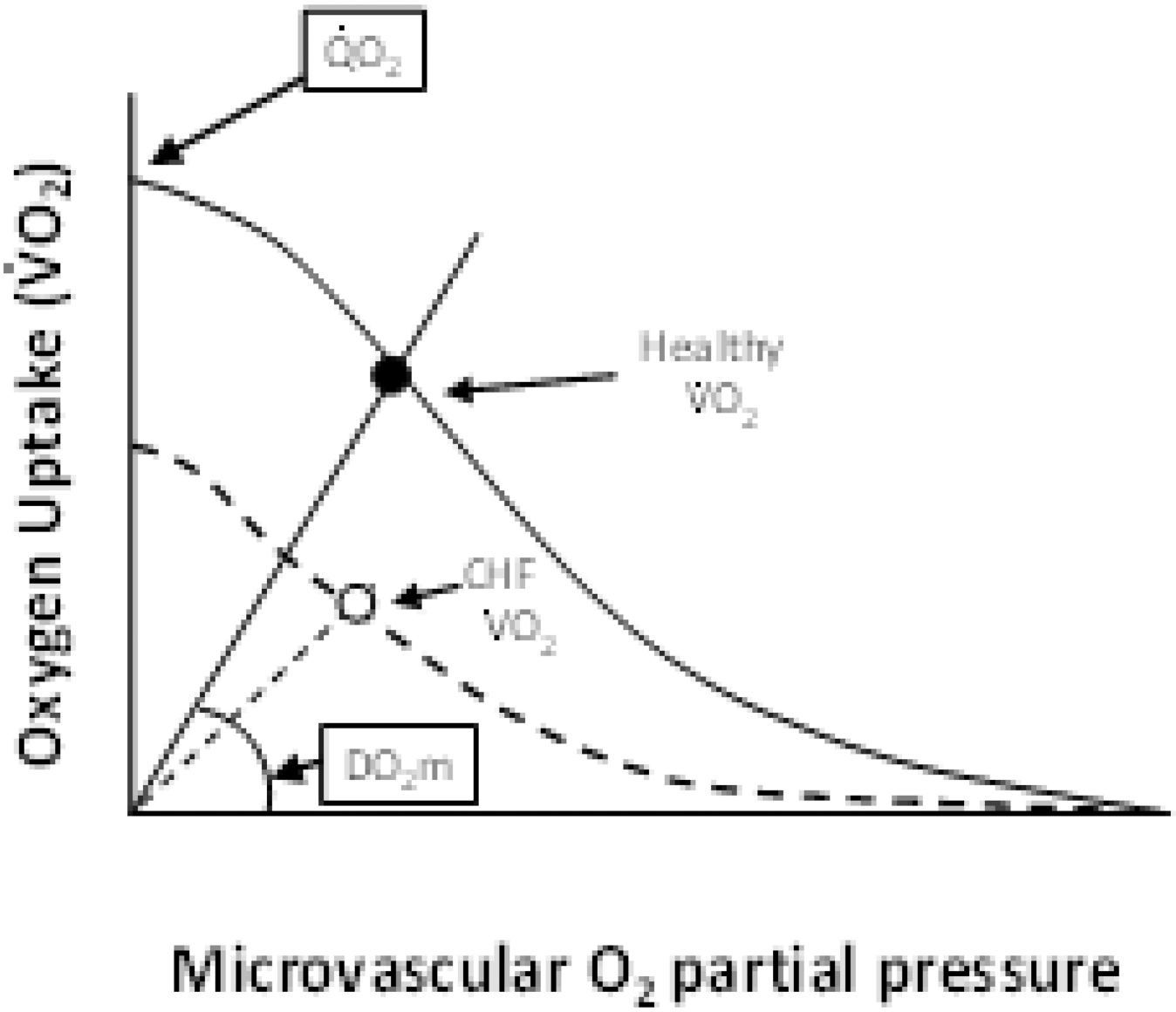

Figure 2.

Schematic illustrating how the muscle perfusive (curved lines, Fick principle, VO_2 = Qm x (arterial-venous O_2 content) and diffusive O2 (straight lines from origin, Fick's law, VO_2 = DO_2m x (PmicrovascularO_2 – PintracellularO_2) conductances conflate to yield VO_2 during exercise (e.g., cycling). In chronic HF (dashed lines) VO_2 is reduced by both impaired perfusive and diffusive O_2 conductances and microvascular O_2 partial pressures may either be the same or lower than found in health notwithstanding the presence of marked diffusional derangements (i.e., lower DO_2m). Note that correction of DO_2m deficits by improving capillary hemodynamics has the potential to increase VO_2 even in the absence of improved muscle perfusion. From reference 37.

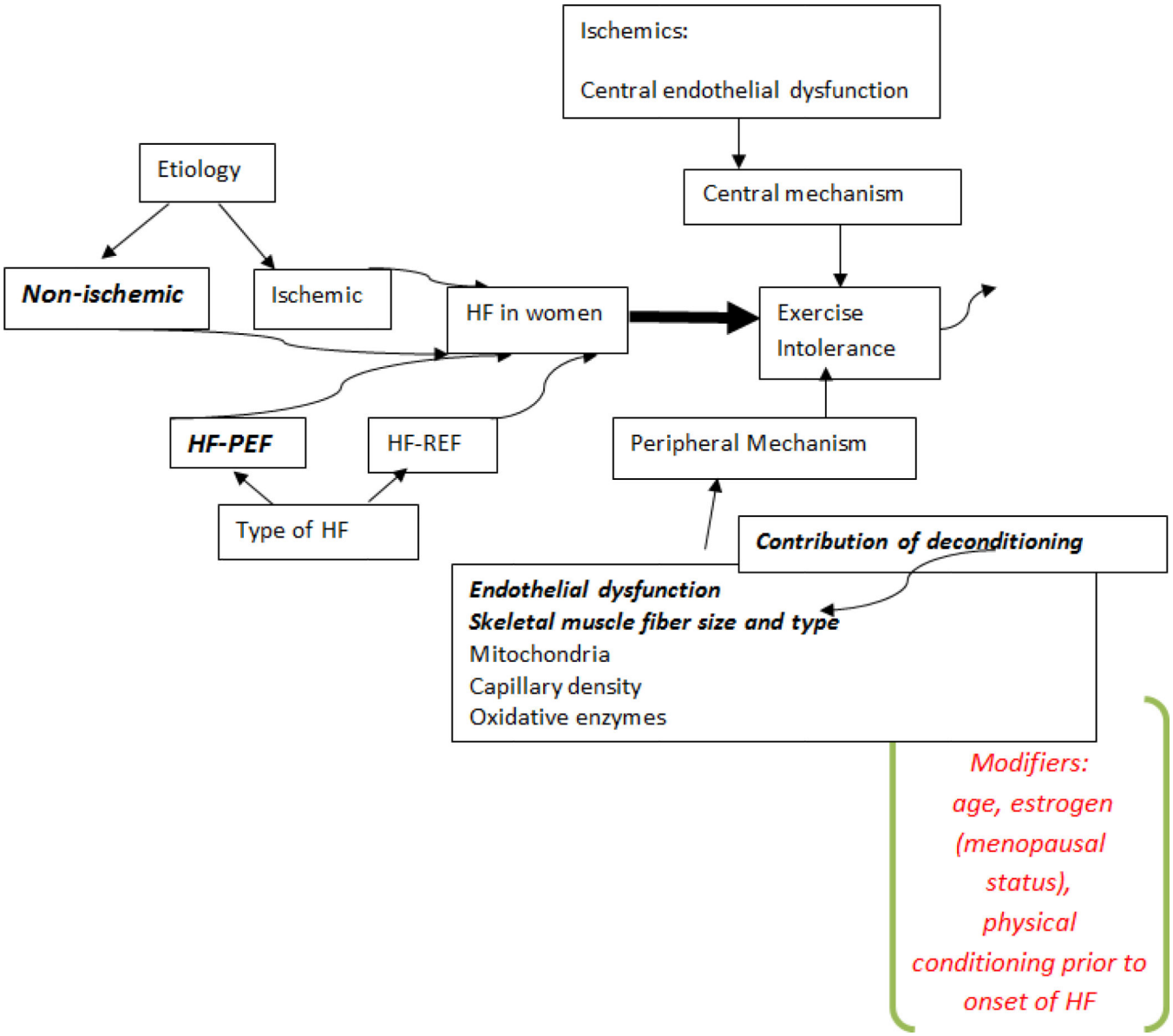

Figure 3.

Possible mechanisms of exercise intolerance in HF as related to gender. Areas that have been associated with women are in bold. The modifiers of the responses are in red in italics. Thus, age may have a more profound effect on the exercise intolerance of women with HF as well as the level of fitness prior to disease onset. Estrogen as a modifier has been poorly studied in HF.

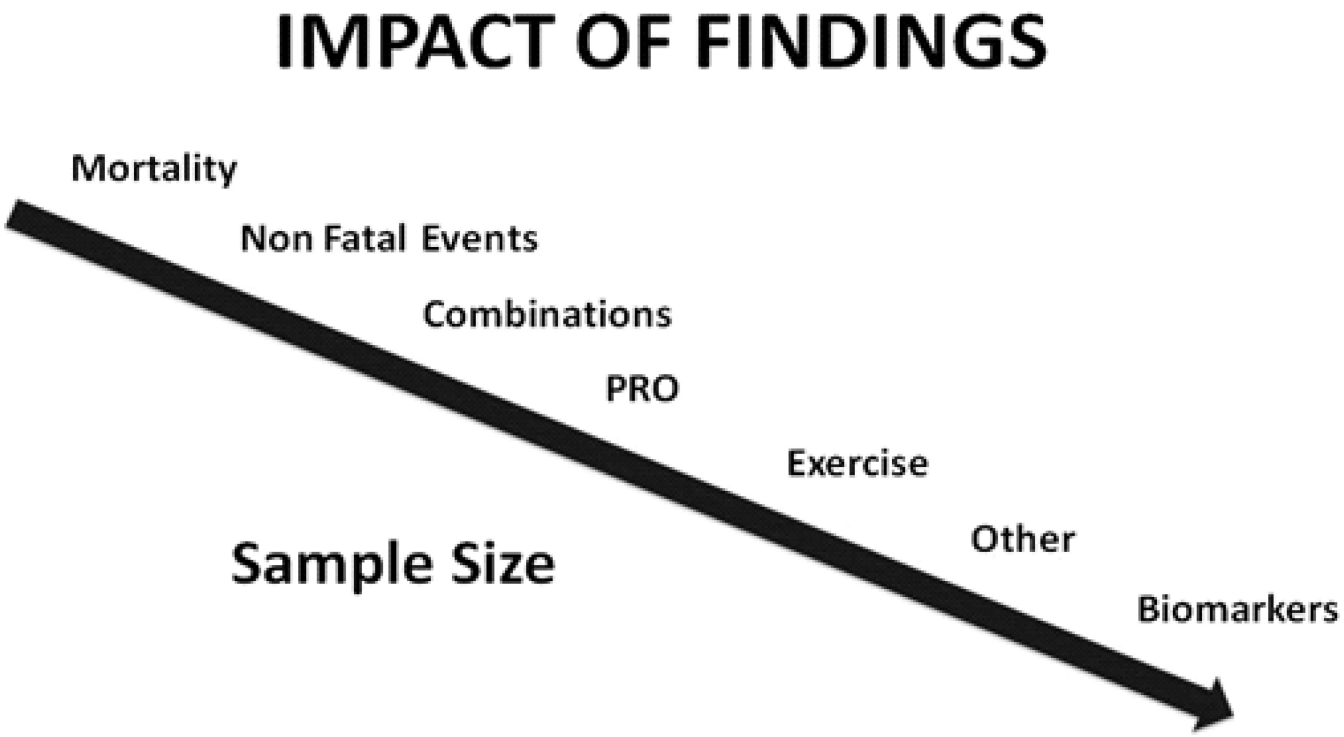

Figure 4.

The figure presents a theoretical hierarchy of possible RCT outcomes and their relationship to the sample size required.

Table

Adherence of Heart Failure Patients to Exercise Training in Some Prior Trials

Trial	Adherence Methodology	Adherence Findings
HF-ACTION (4,5)	Follow-up phone calls and Physical Activity Questionnaire	40% performing exercise training as prescribed at month 3
Coats AJS *et al*.(13)	Percentage of expected bicycle wheel revolutions	Mean adherence 77.3% (range 26–116%)
Evangelista *et al*.(81)	Pedometers (10% improvement in scores)	20/38 (53%) patients found to be adherent
Corvera-Tindel *et al*.(82)	Pedometers (actual walking time/prescribed time)	Mean adherence 74.3±37% (N=42 in exercise training arm)
McKelvie RS *et al*.(83)	Pre-randomization screening	43% attended >80% of sessions, 16% attended <50% of sessions. Patients exercised 2.3±0.4 sessions/wk. during the first[t] month and 1.7±0.4 sessions/wk. by Month 12.
Oka *et al*.(84)	Activity logs and telephone contact	Average adherence 110% for aerobic, 87% for upper body, and 75% for lower body