# EXERCISE AND HEART FAILURE: ADVANCING KNOWLEDGE AND IMPROVING CARE

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**Abstract**

Exercise limitation is the hallmark of heart failure, and an increasing degree of intolerance is associated with poor prognosis. Objective evaluation of functional class (e.g., cardiopulmonary exercise testing) is essential for adequate prognostication in patients with advanced heart failure and for implementing an appropriate exercise training program. A graded exercise program has been shown to be beneficial in patients with heart failure and has become an essential component of comprehensive cardiac rehabilitation in these patients. An exercise program tailored to the patient's preferences, possibilities, and physiologic reserve has the greatest chance of being successful. Despite being safe, effective, and a guideline-recommended treatment to improve quality of life, exercise training remains grossly underutilized. Patient, physician, insurance and practice barriers need to be addressed to improve this quality gap.

## Introduction

Heart Failure (HF) is a progressive clinical syndrome that affects more than 5 million Americans at any given time.[1] Caused by impaired systolic or diastolic performance of the heart, HF is characterized by exercise intolerance due to fatigue and/or shortness of breath.[1,2]

In the first half of the 20th century, bed rest "from days to weeks to months" was recommended for heart failure patients.[3] Subsequently, research into understanding the mechanisms of exercise intolerance led to the development of evidence that supports the favorable effects of exercise training in heart failure patients. Today, exercise training is one of the main components of comprehensive cardiac rehabilitation programs.[4]

The objective of this review is to describe the determinants of exercise limitation in HF, how to assess exercise capacity of HF patients, prognostic implications of exercise intolerance, and essential components of exercise prescription.

## Mechanisms of Exercise Limitation in Heart Failure

The human body's response to exercise involves a complex interaction between lungs, heart, muscles, systemic and pulmonary vasculature. and mitochondrial respiration.[5] From a cardiovascular standpoint, increases in cardiac output (CO) and peripheral vasodilatation (i.e., a decrease in systemic vascular resistance) are crucial for delivering adequate oxygen to meet the body's metabolic demands. Pathophysiological mechanisms of impaired exercise tolerance in HF include decreased contractility, diastolic impairment, increased peripheral resistance, functional mitral regurgitation, chronotropic incompetence, inadequate distribution of blood flow (i.e., failure to direct CO to the exercising muscles), abnormal skeletal muscle metabolism, endothelial dysfunction, and abnormally high ergoreflex activation.[6]

The modulation of sarcomeric function with changes in length described by the Frank-Starling relationship enables beat-to-beat adaptation of CO to increase or decrease preload. Heart failure patients with reduced ejection fraction (HFrEF) have the stroke volume–preload function curve shifted to the right and flattened, reflecting an almost-exhausted preload reserve with relatively fixed stroke volume.[7] In this context, heart rate becomes the main driver to increase CO during exercise. Heart rate reserve is impaired in the vast majority of HF patients. Chronotropic incompetence, which is defined as the inability to increase heart rate proportionally to the degree of metabolic demands, affects between 25% to 70% of patients with HF and is probably related to beta-adrenergic receptor downregulation and desensitization along with sinus node remodeling.[8]

In HF with preserved ejection fraction (HFpEF), chamber stiffness prevents left ventricular (LV) diastolic volume from increasing to accommodate increased venous return. In addition, an abnormal relaxation velocity versus heart rate relationship causes a progressive decrease in lusitropic state as the heart rate increases. Both mechanisms contribute to an increase in LV end diastolic pressure (LVEDP) during exercise.[9]

Comorbid coronary disease is present in more than 60% of patients with HFpEF and HFrEF, and careful evaluation is key in treating this potentially reversible cause of exercise limitation. Myocardial ischemia due to decreased coronary flow reserve has been reported in patients with idiopathic dilated and hypertrophic cardiomyopathy and contributes to impaired cardiac reserve during exercise.[10, 11] Heart failure patients also experience skeletal muscle hypoperfusion from decreased CO and increased peripheral vasoconstriction, which leads to metabolic and structural changes that reduce strength and increase fatigability. Recently, skeletal muscle receptors have been recognized as potential perpetuators of sympathetic hyperactivity.[12] Myopathy of respiratory muscles has been described as a significant contributor of dyspnea and exercise intolerance in HF patients (Figure 1).[13]

## Evaluation of Exercise Capacity

The New York Heart Association (NYHA) Functional Classification was introduced more than 80 years ago to provide a simple way of classifying the degree of exercise limitation in patients with cardiac disease. Heart failure patients are classified according to the severity of their symptoms, as follows:

- NYHA I: No symptoms and no limitations in ordinary physical activity.

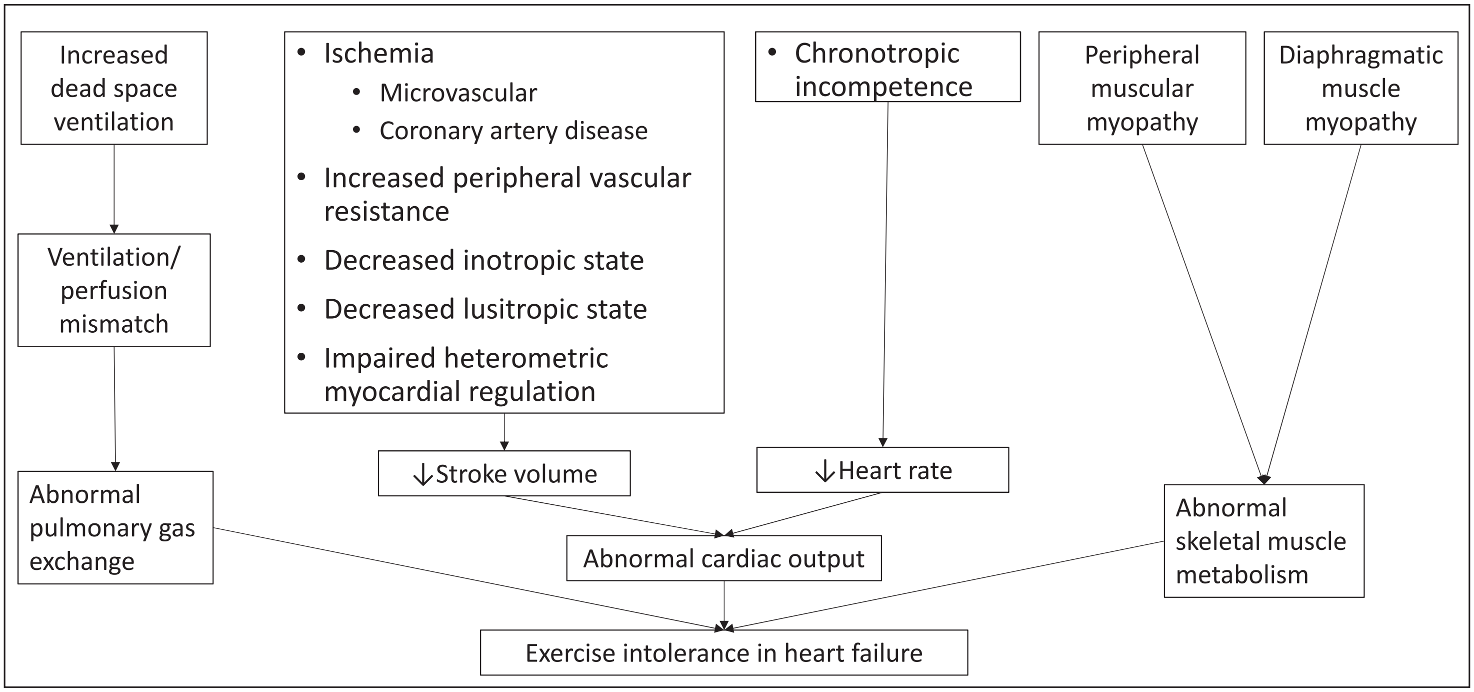


**Figure 1.** Mechanisms involved in exercise intolerance due to heart failure.

- NYHA II: Mild symptoms and slight limitation during ordinary activity.
- NYHA III: Marked limitation in activity due to symptoms of fatigue and dyspnea, even during less-than-ordinary activity; comfortable at rest.
- NYHA IV: Severe limitations and symptoms at rest.

Although useful for an initial ball park evaluation, the subjective nature of this system and the difficulty in recognizing intermediate functional classes (II-III) limits its precision.[14]

Table 1 summarizes a variety of tests including stair climb, shuffle test, 6-minute walk test (SMWT), exercise electrocardiography, and cardiopulmonary exercise testing (CPET) that allow quantitative evaluation of exercise capacity. The SMWT and CPET are the most studied objective measures. The SMWT is a standardized, reproducible, low-tech test of exercise capacity that measures the distance a patient can walk on a flat, hard surface in 6 minutes. It requires minimal equipment and no specific training of the technician performing the study. Given the self-paced nature of the study, results depend heavily on the motivation of the

| Type | Intensity | Evaluation | Standardized | Reproducible | Comments |
|---|---|---|---|---|---|
| Stair climb test | Near maximal | Functional capacity | No | No | Climbing > 1 flight of stairs without stopping > 4 METS. |
| Incremental shuttle test | Near maximal | Functional capacity | Yes | Yes | Patients are required to walk at a speed dictated by audio signals from an audio tape recorder. The walking speed is progressively increased. Good correlation with peak $VO_2$ |
| Six minute walk test | Near maximal | Functional capacity | Yes | Yes | Useful in patients with moderate to severe impairment. Extensive experience in patients with pulmonary and cardiac disease. Used to assess response to interventions. |
| Exercise electrocardiography | Maximal | Ischemia and exercise duration | Yes | No* | Analysis of heart rate response to exercise and heart rate recovery permit the evaluation of chronotropic incompetence and autonomic dysfunction with additive prognostic information. |
| Cardiopulmonary stress testing | Maximal | Peak $VO_2$ and exercise duration. | Yes | Yes | Gold standard. Incorporated in AHA/ACC and ISHLT guidelines for the evaluation of patients with advance heart failure. Not widely available. Trained staff required and specialized equipment. |
| *Probably related to the large intra-individual variability of electrocardiographic recordings at rest. | | | | | |

**Table 1.** Clinical exercise tests.

| Meta-analysis (ref) | ExTraMATCH[26] | Davies[27] | Sagar[28] |
|---|---|---|---|
| **Year** | 2004 | 2010 | 2014 |
| **Number of patients** | 801 | 3,647 | 4,740 |
| **Number of trials** | 9 | 19 | 33 |
| **Intervention** | Aerobic | Aerobic. Five trials resistance training. | Aerobic. Eleven trials resistance training |
| **Conclusions** | Safe and reduces mortality. | Decreased heart failure-related hospitalization, improved quality of life. No significant difference in short- or long-term mortality. | Decreased overall and heart failure-related admissions, no effect on mortality. Exercise also improved quality of life. |
| ExTraMATCH: Exercise training meta-analysis of trials in patients with chronic heart failure | | | |

**Table 2.** Meta-analysis of exercise training in heart failure with reduced ejection fraction.

patient performing the test. Overall, the SMWT provides a global evaluation of the systems involved in exercise tolerance.[15] Recently self-administered SMWT using a smartphone application has been reported with promising results.[16]

CPET requires specialized equipment and training of the technician performing the study and the physician interpreting the results. This highly standardized and reproducible test measures gas exchange patterns, allowing the physician to determine which organ system is limiting exercise capacity.[17,18] Relevant parameters measured during CPET include:

- Peak/maximal oxygen uptake (peak $VO_2$): measures the maximal ability of the body to transport and utilize $O_2$; defines the limit of the cardiopulmonary system, is expressed in milliliters of oxygen per kilogram of body weight per minute, and depends on effort, age, and gender; the prognosis is worse in patients with HF if peak $VO_2 < 10$ mL/kg/min.
- Ventilatory derived anaerobic threshold ($VO_2$ at VT): the point during exercise when there is a disproportionate increase in energy production from anaerobic metabolism.
- Respiratory exchange ratio ($VCO_2/VO_2$): overall indicator of cardiorespiratory stress and a measure of subject effort; acceptable if ratio values > 1.1.
- Ventilatory efficiency ($V_E/VCO_2$ slope): represents the perfusion that is matched to ventilation; independent of subject effort, worse prognosis if slope is > 34.
- Other important parameters include blood pressure, heart rate response, exercise duration, continuous electrocardiographic monitoring, and pulmonary function tests.

The interpretation of CPET involves integrating all the parameters and considering additional comorbidities such as anemia, obesity, lung diseases, and skeletal limitations. The insertion of a pulmonary artery catheter and arterial line before CPET may be considered when the cause of exercise limitation is not clear.[23]

## Exercise as a Prognostic Tool

The presence of symptoms in patients with LV systolic dysfunction is a powerful negative prognostic indicator. For example, in the Studies of Left Ventricular Dysfunction (SOLVD) prevention and treatment trials, the 3-year mortality rates in the placebo group were 15% and 39%, respectively.[19,20] The correlation between NYHA functional class and mortality has also been reported in patients with HFpEF.[21] Fatigue, which is a vague symptom and very difficult to quantify, has been associated with an increased risk of hospitalization.[22] Exercise limitation can be further quantified using CPET, which is a standard of care in HF clinics when evaluating a patient's candidacy for transplant or mechanical device. Currently accepted thresholds of $VO_2$ to be considered for either of these advanced HF therapies are 14 mL/kg/min off beta blockers and < 12 mL/kg/min on beta blockers.[24] The prognostic value of CPET has been recently revisited and confirmed in a secondary analysis of the HF action trial.[23] A recent secondary analysis of HF-ACTION trial showed that peak $VO_2$, exercise duration, and percent predicted peak $VO_2$% carried the strongest ability to predict and discriminate the likelihood of death in patients with HFrEF. Another important finding of the same report was that prognosis associated with a given peak $VO_2$ differed by sex. For example, a peak $VO_2$ that corresponded to a 10% 1-year all-cause mortality was 10.9 mL/kg/min and 5.3 mL/kg/min in men and women respectively.

## Exercise as a Therapeutic Intervention

Exercise training is defined as "exercise performed repetitively to increase the performance capacity of the cardiovascular system (aerobic exercise training) or muscular skeletal system (resistance exercise training)."[24] The benefits of exercise training in HF patients have been well documented. Results from systematic reviews and meta-analyses have shown that exercise training is not only safe but also is associated with a reduced risk of hospitalization and a decrease in mortality (Table 2).[25-27] HF-ACTION was the largest multicenter randomized controlled trial of exercise training in HF. It included patients with HFrEF who were classified as NYHA II-IV, and it demonstrated the safety of exercise training. Hospitalizations after exercise occurred in 3.2% of the patients assigned to the supervised exercise program. The most frequent obstacle to achieving the duration or intensity goal in at least one supervised exercise session was angina, followed by arrhythmia, pre-syncope or syncope, and hypoglycemia.[28] The trial failed to show efficacy in all comers, but when adjusted for other prognostic variables, exercise training was associated with decreased all-cause mortality and hospitalization (HR = 0.89; 95% CI, 0.81-0.99; $P = .03$) and heart failure readmissions and HF-related mortality (HR = 0.85; 95% CI, 0.74-0.99; $P = .03$). Increasing the duration of supervised exercise training may be fundamental for the benefits of exercise training (Table 3).[29] Current guidelines state, "Exercise training (or regular physical activity) is recommended as safe and effective for patients with HF who are able to participate to improve functional

| Trial (ref) | Belardinelli[30] | HF-ACTION[29] |
|---|---|---|
| Number of patients | 123 | 2,331 |
| Population | 59 years of age | 59 years of age |
| | 27% women | 28% women |
| | NYHA II/III (100%) | NYHA II/III (99%) |
| | mean EF 37% | median EF 25% |
| Follow-up | 10 years | 30.1 months |
| Intervention | 60% of peak $VO_2$, 2x/week for 6 months followed by 70% of peak $VO_2$, 3x/week for the rest of study (10 yrs).<br>Patients exercised at coronary club for the duration of the study, with supervised sessions every 6 months. | Stage I: supervised. 60% of heart rate reserved, 3x/week for 2 weeks for 15-30 min followed by 70% of heart rate reserved, 3x/week for 30-35 min for total of 3 months.<br>Stage II: home-based. 60-70% of heart rate reserved 5x/week for 40 min. |
| Outcomes | Increased peak $VO_2$, improved quality of life, decreased hospital readmission, decreased cardiovascular mortality | No reduction in all-cause mortality or hospitalization. |
| NYHA: New York Heart Association; EF: ejection fraction; $VO_2$: oxygen consumption | | |

**Table 3.** Landmark trials of exercise training in heart failure.

status Class IA."[30] Despite this recommendation, only 10.4% of eligible HF patients received cardiac rehabilitation referral after hospitalization for HF.[31]

On February 18, 2014, the Centers for Medicare and Medicaid Services (CMS) expanded coverage for cardiac rehabilitation services to "beneficiaries with stable, chronic heart failure, defined as patients with left ventricular ejection fraction of 35% or less and New York Heart Association (NYHA) class II to IV symptoms despite being on optimal heart failure therapy for at least six weeks. Stable patients are defined as patients who have not had recent (≤ 6 weeks) or planned (≤ 6 months) major cardiovascular hospitalizations or procedures."[32]

## Main Components of an Exercise Prescription for Heart Failure Patients

Once contraindications to exercise therapy have been excluded and potential reversible causes of exercise intolerance (e.g., decompensated heart failure, anemia, endocrine disorders) have been treated, an exercise prescription can be made (Figure 1). This involves assessing the energy cost of the activity that is being planned and whether or not the patient is able to safely exercise at that specific level. The patient should perform a symptom-limited graded exercise test, preferably a CPET, which can provide key information about that patient's specific goals.[33] This quantitative approach allows precise recommendations of the level of exercise. A moderate level, which is the most often prescribe, is defined as 40% to 60% of heart rate reserve (peak heart rate minus resting heart rate), 40% to 60% of the $VO_2$ reserve (peak $VO_2$ minus resting $VO_2$), and a rating of perceived exertion 12 to 13.

Clinical variables such as age, gender, comorbidities, previous physical activity, and orthopedic/musculoskeletal factors must be considered when tailoring an appropriate exercise plan. There are several patient and therapy related barriers to exercise therapy, therefore, the physician should carefully address any obstacles to compliance (as is done with drug therapies), empower the patient with information about the efficacy and safety of exercise therapy, follow up with the patient's exercise plan during every visit, and encourage the patient on his or her accomplishments.[34]

Currently, CMS covers 36 sessions of cardiac rehabilitation, after which the patient must continue with unsupervised exercise training, adding several challenges for compliance.

## Exercise Training in Special Heart Failure Patient Populations

### *Heart Failure with Preserved Ejection Fraction*

In a recent meta-analysis including 276 patients with HFpEF, exercise training was associated with improved cardiorespiratory fitness as measured by peak oxygen uptake and quality of life.[35] The mechanism by which this is achieved is through improvement of peripheral factors such as skeletal muscle function, endothelial function, and arterial stiffness.[36]

### *Heart Transplant*

After heart transplantation, patients remain with significant exercise intolerance when compared with an age- and sex-matched healthy population. This is related mainly to the persistence of peripheral factors including skeletal muscle dysfunction and impaired vasodilatory capacity. Lack of autonomic innervation also contributes to abnormal heart rate response. Exercise therapy has consistently been associated with an improvement in peak $VO_2$, however, the optimal type of therapy remains to be defined.[37]

### *Left Ventricular Assist Devices*

The effect of exercise on patients with left ventricular assist devices (LVAD) has been inconsistent throughout the literature, partly due to the heterogeneity of the studies and the small sample sizes. While some authors found that exercise did not lead to improvement in peak $VO_2$, others found that it does improve peak $VO_2$ as well as quality of life. Early progressive mobilization can safely be started 1 week after LVAD implantation and exercise training can be started after 2 to 4 weeks, with maximal improvement in exercise capacity after 12 weeks.[38]

## Conclusion

Exercise intolerance is common in patients with heart failure and is multifactorial in causation. Exercise therapy is

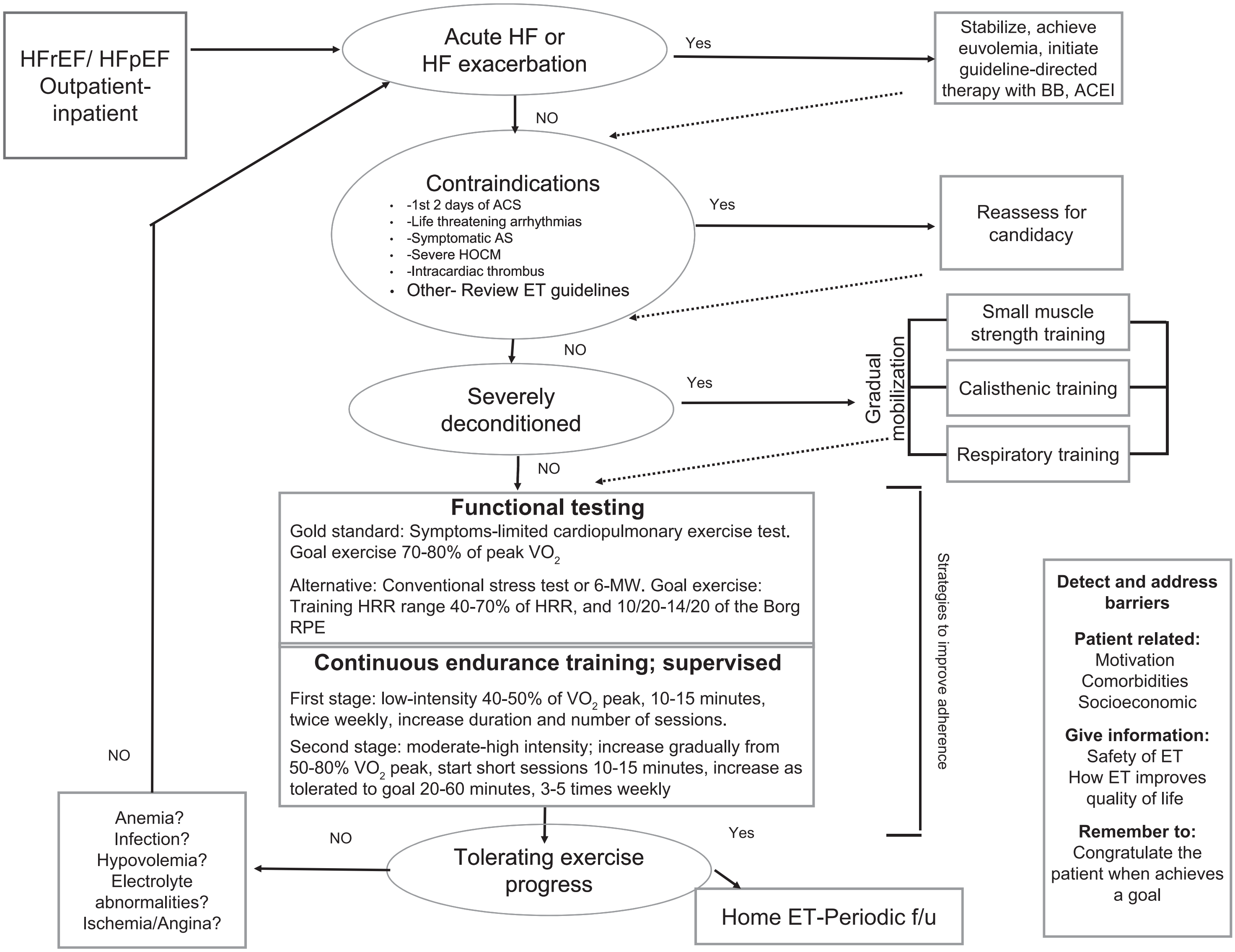


**Figure 2.** Approach to exercise training prescription.
HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; HF: heart failure; BB: beta blocker; ACEI: angiotensin converting enzyme inhibitor; ACS: acute coronary syndrome; AS: aortic stenosis; HOCM: hypertrophic obstructive cardiomyopathy; $VO_2$: oxygen consumption; ET: exercise training; f/u: follow-up

one of the most effective, safe, and underutilized treatments for exercise intolerance in HF. Recognition of patient and practice barriers for exercise therapy program implementation is important to help close this prevalent quality gap in the care of HF patients.

## Key Points:

- Exercise training is an essential component of comprehensive cardiac rehabilitation.
- Exercise training is a safe, effective, and guideline-recommended treatment to improve quality of life and morbidity in patients with heart failure.
- Objective evaluation of functional class should be performed early on in the assessment of patients with heart failure, regardless of their left ventricular ejection fraction.
- Tailoring an exercise program to the patient's preferences, abilities, and physiologic reserve increases satisfaction and adherence.
- Successful implementation of an exercise program depends on recognizing and addressing patient, physician, insurance, and practice barriers.

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**Keywords:** heart failure, exercise, cardiopulmonary exercise testing

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