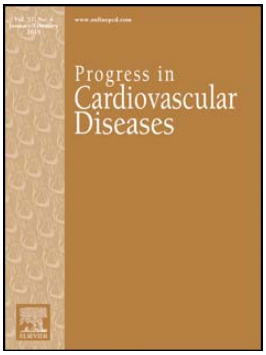

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Exercise Training in Group 2 Pulmonary Hypertension: Which Intensity and What Modality

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Abbreviations:

CO- Cardiac output

ET- Exercise training

HF – Heart failure

HFpEF – Heart failure preserved ejection fraction

HFrEF – Heart failure reduced ejection fraction

HIIT – High intensity interval training

IMT- Inspiratory muscle training

LSHD- Left-sided heart disease

LV – Left ventricle or ventricular

NMES- Neuromuscular electrical stimulation

PAP – Pulmonary artery pressure

PH – Pulmonary hypertension

QoL- Quality of life

RV – Right ventricle or ventricular

VO_2 – Oxygen consumption

Abstract

Pulmonary hypertension (PH) due to left-sided heart disease (LSHD) is a common and disconcerting occurrence. For example, both heart failure (HF) with preserved and reduced ejection fraction (HFpEF and HFrEF) often lead to PH as a consequence of a chronic elevation in left atrial filling pressure. A wealth of literature demonstrates the value of exercise training (ET) in patients with LSHD, which is particularly robust in patients with HFrEF and growing in patients with HFpEF. While the effects of ET have not been specifically explored in the LSHD – PH phenotype (i.e., composite pathophysiologic characteristics of patient's in this advanced disease state), the overall body of evidence supports clinical application in this subgroup. Moderate intensity aerobic ET significantly improves peak oxygen consumption, quality of life and prognosis in patients with HF. Resistance ET significantly improves muscle strength and endurance in patients with HF, which further enhance functional capacity. When warranted, inspiratory muscle training and neuromuscular electrical stimulation are becoming recognized as important components of a comprehensive rehabilitation program. This review will provide a detailed account of ET programing considerations in patients with LSHD with a particular focus on those concomitantly diagnosed with PH.

Key words: Aerobic exercise; resistance exercise; inspiratory muscle training; functional capacity;Pulmonary Hypertension

Pulmonary hypertension (PH) due to left-sided heart disease (LSHD) is a disconcerting occurrence with important clinical implications.[1, 2] Heart failure (HF), mitral/aortic valvular disease and hypertrophic cardiomyopathy are three prime examples of LSHD that may lead to PH. The manifestation of PH with LSHD is a clear indication of advanced disease severity with poor prognosis. Of the three aforementioned conditions, HF has the highest profile given the high incidence (United States: >850,000 new cases per year) and prevalence (United States: >5.5 million patients currently diagnosed) of this condition.[3] Both HF with reduced and preserved ejection fraction (HFrEF and HFpEF) can lead to PH as a consequence of a chronic elevation in left atrial filling pressure. In fact, PH in patients with HF is a common occurrence that coincides with disease progression, with an estimated prevalence of ~60% in the HF population (HFrEF and HFpEF combined).[4]

Exercise training (ET) is now widely accepted as an important medical intervention (i.e., exercise is medicine).[5] There is a wealth of literature demonstrating the value of ET in patients with LSHD; the body of evidence is particularly robust in patients with HFrEF and quickly growing in patients with HFpEF.[6-10] The research conducted in this area allows us to understand a number of facets associated with ET in HF, including: 1) a host of expected positive physiologic adaptations; 2) expected clinical improvements; and 3) improvements in prognosis. In addition, research conducted in this area also allows for clear clinical guidance on approaches to ET prescription (i.e., frequency, intensity, type and time). Even so, there are clear knowledge gaps where additional research is needed.

The current review describes the mechanisms for exercise intolerance as well as ET considerations in patients with LSHD, particularly within the context of associated PH. This review focuses on the HF model, given the current incidence and prevalence of this condition, as

well as the high risk of developing PH once this diagnosis is established. Clinically relevant guidance on approaches to ET in patients with LSHD are provided as well as recommendations for future research in this area.

Pathophysiologic Mechanisms of Exercise Intolerance in LSHD

The augmentation of left-sided cardiac output (CO) during physical exertion is the primary determinant of variation in aerobic capacity from one individual to another, as described by the Fick equation.[11-14] As such, the primary pathology of LSHD, left ventricular (LV) dysfunction that results in reduced CO, is a central explanatory factor for the diminished aerobic capacity that is observed in this patient population. This is a commonality shared amongst all left-sided conditions: 1) HFrEF and HFpEF; 2) Mitral/Aortic valve disease/dysfunction; and 3) hypertrophic cardiomyopathy. Moreover, as the severity of the LSHD worsens, CO and, therefore, aerobic capacity falls in parallel. Clinically significant LSHD, past the initial mild stages, makes attainment of a normal age- and sex-predicted aerobic capacity virtually impossible.

The development of PH in patients with LSHD may further exacerbate the decline in left-sided CO by: 1) decreasing transmission of blood flow from pulmonary circulation to the LV as a function of increasing pulmonary artery pressure (PAP); 2) a potential leftward shift of the septal wall induced by an increasing PAP that impacts LV filling; and 3) chronic damage to the alveolar-capillary interface, impacting gas exchange.[1, 15] This is a function of a multifactorial deleterious impact on pulmonary gas exchange and LV CO during exertion.

The pathophysiologic milieu that significantly impacts diminished aerobic capacity in LSHD extends beyond the central cardiopulmonary circuit; these alterations have been thoroughly examined in the HF model. Specific detrimental effects are as follows: 1) The

vasodilatory capacity of the peripheral vasculature is diminished, impacting availability of oxygenated blood for aerobic energy metabolism in working skeletal muscle; 2) Skeletal muscle function is altered, with diminished aerobic energy production (i.e., decreased mitochondrial capacity) as well as muscular strength and endurance (i.e., muscle fiber atrophy and diminished muscle mass); and 3) The presence of respiratory muscle weakness, resulting in the onset of respiratory muscle fatigue and dyspnea during aerobic exercise.[8, 16, 17] These detrimental changes to the peripheral vasculature, skeletal muscle and respiratory muscle systems combine with cardiopulmonary pathophysiology to meaningfully impact functional capacity in patients with LSHD, often to profound levels.

The detrimental impact of the LSHD process on the physiologic systems highlighted in this section is well characterized in the HF model, a common cause of group 2 PH[4] that denotes an advanced stage. Thus, the collective physiologic derangements described in this section are more likely to be present and highly evolved in patients with a LSHD – PH phenotype, which has been eloquently described in those diagnosed with HF.[1, 4, 18] Moreover, patients with LSHD and concomitant PH commonly demonstrate a very poor tolerance to physical exertion.

The Physiologic Effect of ET in Patients with LSHD

Indeed, ET portends a host of physiologic benefits in virtually all individuals across the continuum of care, from primordial prevention in the community to secondary prevention in those diagnosed with a chronic disease, the latter includes those patients diagnosed with LSHD.[11] Certain physiologic benefits of ET are well documented in the HF model[16]; most of this work has been done in patients with HFrEF although research in this area is rapidly expanding in the HFpEF model.

Moderate Intensity Aerobic ET

The ET intervention most frequently examined in the literature is moderate intensity aerobic ET that spans several weeks to months. The mode of ET is commonly a treadmill, lower extremity ergometer, walking program, or a combination thereof; ET durations in these studies typically range from 30 to 60 minutes per session, 3-5 days per week.

Most evidence indicates LV systolic function (i.e., CO) does not seem to meaningfully improve with moderate intensity ET.[8, 19, 20] There is some evidence to suggest an improvement in diastolic function following ET, although results are mixed in patients with both HFrEF[6, 8, 21] and HFpEF[7, 22, 23]. With respect to other LSHD associated with PH, there is limited analysis on the effect of moderate intensity ET on cardiac function; a recent review called for this type of research in patients with hypertrophic cardiomyopathy.[24]

Peripherally, the documented physiologic adaptations associated with moderate intensity aerobic ET are much clearer; this again has been extensively studied in the HF model, particularly those with HFrEF.[8, 16, 17, 25] There is a clear improvement in skeletal muscle characteristics, favoring an improvement in aerobic energy metabolism. There is also strong evidence to indicate an improvement in peripheral vascular function, specifically an enhanced endothelial function and vasodilatory capacity in patients with HFrEF. The improvement in endothelial function in patients with HFpEF is less clear.[26]

Patients with HF develop unfavorable autonomic nervous system characteristics and have elevated systemic inflammation, the latter of which demonstrated by several markers including tumor necrosis factor and interleukin-6. These alterations contribute to the downward spiral in physiologic systems vital to exercise performance (i.e., cardiac, vascular and skeletal muscle function). Moderate intensity aerobic ET significantly increases vagal tone and reduces systemic inflammation in patients with HF.[8, 19] These favorable adaptations induced by ET have clear

benefits to preserving/improving function of the physiologic systems that dictate aerobic exercise performance.

Aerobic High Intensity Interval ET (HIIT)

There has been a growing interest in aerobic HIIT in patients with HF.[27-32] This approach entails 30 second to 4 minute cycles of ET at near maximal aerobic capacity [i.e., ≈90% of peak oxygen consumption (VO_2) or maximal heart rate] interspersed with cycles at a substantially lower intensity ET(i.e., complete rest to ≈50% of aerobic capacity). A clear consensus on the optimal HIIT training model has yet to be elucidated, although longer on/off cycles (e.g., 3 minute on - 3 minute off) is more frequently employed. From a physiologic perspective, the most compelling evidence for utilization of this approach is the documented improvements in LV remodeling and function (i.e., CO).[30] The majority of evidence demonstrating superior central adaptations with HIIT compared to moderate intensity aerobic ET has been performed in HFrEF cohorts. There is initial evidence to indicate HIIT also produces enhanced improvements in left-sided diastolic function in patients with HFpEF.[27] Improvements in vascular and skeletal muscle function may also be superior following HIIT compared to moderate intensity ET.[30] However, while evidence continues to mount, HIIT still requires further exploration before definitive clinical recommendations regarding its utility can be made; trials are ongoing to further determine the clinical applicability of HIIT in patients with LSHD, specifically those diagnosed with HF.[28]

Resistance ET

Resistance ET in HF, typically in the form of moderate intensity (i.e., ≈50% of 1 repetition maximum), high repetition (i.e., 10-12 repetitions), multi-joint exercises, significantly improves muscle mass and muscle fiber contractile properties in patients with HF, resulting in

improvements in both force production and endurance.[17, 33, 34] Resistance ET also appears to significantly improve endothelial function. Moreover, there appears to be no detrimental effects to cardiac function in HF patients who participate in moderate intensity resistance ET.[34]

Inspiratory Muscle Training

Inspiratory muscle training (IMT), performed 3-7 days per week, 15-30 minutes per session, at 30-60% of mean inspiratory pressure, improves respiratory muscle dysfunction induced by HF, increasing both the force production and endurance of this system; this has primarily been studied in cohorts with HFrEF.[35] There is also an "unloading" of the respiratory musculature through IMT, which improves peripheral blood flow to exercising skeletal muscle.[36, 37] In addition, IMT has demonstrated numerous additional positive adaptations in an animal model including: 1) reduced LV diastolic pressure; 2) increased LV systolic pressure; 3) decreased right ventricular (RV) hypertrophy; and 4) vagal tone.[38]

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation (NMES) delivers rhythmic electrical impulses to several large muscle groups that is sufficient to induce a muscle contraction; the magnitude of the stimulus delivered is to patient tolerance. The muscle groups most frequently undergoing an NMES intervention in previous studies are the quadriceps, calves, and hamstrings. A NMES program increases skeletal muscle mass as well as the aerobic and contractile properties of individual fibers.[17, 39] In addition, endothelial function[40] is improved and systemic inflammation[41] is reduced following an NMES intervention. The physiologic improvements appear to be greatest in those patients with advanced HF severity.[42] Recent guidelines endorse the use of NMES in HF patients with severe functional deficits.[43]

Does ET Impact PH in LSHD?

The impact of ET on pulmonary hemodynamics in the LSHD– PH phenotype has not been investigated. Our group recently published a review on the effect of ET on PH from mechanisms other than LSHD; both animal and human models were assessed.[44] The ET interventions in these studies were either combined aerobic, resistance and respiratory training interventions (7 human studies) or solely aerobic ET interventions (4 animal studies); these programs were considered to be within the moderate intensity range. The length of training interventions ranged from 3-15 weeks. As endpoints, these studies assessed endothelium dependent relaxation, PAP and pulmonary vessel wall characteristics pre and post training. Only 2 of the 7 human studies found an improvement in pulmonary hemodynamics following ET. In the animal studies, 2 of the 4 demonstrated positive adaptations in pulmonary vessel wall characteristics and hemodynamics while the other two demonstrated no improvement. One Winstar rat model study assessed the effects of ET in both a stable and progressive PH cohort. While there was a significant improvement in CO and peripheral vascular resistance in the stable PH group, there was deterioration in both hemodynamic measures in the progressive PH group. From the current body of literature, the effect of ET on pulmonary hemodynamics and vessel wall characteristics in humans and animals with PH, from conditions other than LSHD, is inconclusive. There was no deterioration in pulmonary hemodynamics or cardiac function in the human trials assessed as well as in the animal trials that included a stable PH arm. In the one trial that included a progressive PH arm, ET induced a detrimental effect.

Should there be concern for an ET-Induced Deterioration in RV Function in the LSHD – PH Phenotype

While the effect of ET on left-sided cardiac function has been well investigated, little is known about possible effects on the right side of the heart, specifically RV function. In patients

with PH, the rise in PAP during exercise can exceed RV capacity, placing an added strain on an already fragile system.[45-47] The question then becomes, what is the effect of chronic ET on RV function in the LSHD – PH phenotype? This question is unanswerable at this time. **Figure 1** illustrates a conceptual model in apparently healthy individuals and those with the LSHD – PH phenotype; linking differences in the pulmonary vascular response to exercise, the PAP – CO relationship, and potential chronic implications for RV function. In **Figure 1**, questions remain regarding chronic adaptations and function of the RV in both apparently healthy individuals and patients with the LSHD – PH phenotype. A primary issue surrounding the long-term effects of ET on RV function in the LSHD – PH phenotype center on the cumulative effect of ET intensity/volume. Research assessing the safety of ET in HF is robust and consistently points to moderate aerobic ET and resistance ET, as well as IMT, as being safe and not causing a deterioration in left-sided cardiac function. Given the high prevalence of PH in HF, it is a certainty that a number of patients undergoing ET in these trials also suffered from varying degrees of elevated PAP. While not directly assessed in these trials, there is no evidence to indicate RV function is compromised with participation in moderate intensity ET, even in the LSHD – PH phenotype. Even so, determination of RV function during moderate intensity ET in theLSHD – PH phenotype, particularly with long-term participation, requires confirmation. Moreover, there could be a greater concern with a deterioration in RV function for patients with the LSHD – PH phenotype that participate in aerobic HIIT, which is gaining increased interest in patients with HF. In fact, there is evidence to convincingly indicate that healthy individuals who participate in high volume/intensity ET chronically have a greater likelihood of disproportionate and potentially deleterious remodeling of the RV.[48-50] Thus, it is reasonable to posit there may be a chronic ET volume/intensity that may be detrimental to the RV in patients with the LSHD –

PH phenotype, particularly given the rise in PAP and strain placed upon the RV in these individuals.

The Clinical Benefits of ET in Patients with LSHD

The clinical benefits of ET in LSHD, particularly in patients with HF, is well-documented and robust.[8, 10, 19, 34, 51] These well-documented clinical benefits form the basis for recommending ET, particularly aerobic and resistance ET, as a standard of care in this population.

Moderate intensity aerobic ET significantly improves peak VO_2, submaximal exercise tolerance and quality of life (QoL).[17, 52] There is evidence to indicate, in select patient cohorts, HIIT results a significantly greater improvement in peak VO_2 compared to moderate intensity aerobic ET,[28]which also appears to improve prognosis in patients with HF. Resistance ET significantly improves muscle strength and endurance in patients with HF, these are unique and added beneficial adaptations that further enhance functional capacity.[34] Resistance ET also significantly improves QoL and peak VO_2, the latter of which is a unique benefit to patients diagnosed with a chronic disease such a HF. In patients with inspiratory muscle weakness, IMT independently and significantly improves peak VO_2 and QoL.[53-55] While not superior to traditional training approaches, NMES has been shown to significantly improve peak VO_2, muscular strength and endurance, as well as QoL.[39, 56] The benefits of NMES appears to be enhanced in HF patients with advanced disease severity.[42]

Current ET Recommendations in LSHD

Table 1 lists current training recommendations for clinically stable patients with LSHD based upon best evidence. These recommendations were included in a recent publication on guidance for ET in patients with chronic obstructive pulmonary disease and PH associated with

any pathophysiologic process[57]. The current body of evidence, assessing the physiologic and clinical benefits of ET, as well as safety associated with ET, support the same recommendations for patients with LSHD. These recommendations are also valid for the LSHD – PH phenotype.

Current recommendations do indicate moderate intensity aerobic ET performed most if not all days of the week is ideal. However, substantial clinical improvements are possible at ET volumes below these recommendations.[58] We are, therefore, continuing to endorse some flexibility in this component of ET prescription. Moderate intensity aerobic ET should be viewed as a primary component of the ET program, and for those who are beginning an ET regimen from a sedentary status, initiating the aerobic ET component exclusively to build a foundation may be preferable. While evidence for the benefits of aerobic HIIT is compelling, more research and clinical work is needed to determine appropriate clinical application. In particular, with respect to the LSHD – PH phenotype, there may be concern over the impact of aerobic ET at high intensities on RV function. As such, we feel continuing to recommend moderate intensity continuous aerobic ET, particularly given its well-demonstrated benefit, is warranted. Resistance ET carries unique benefits and should be added to the aerobic ET program in all patients. For those with inspiratory muscle weakness, the addition of IMT would be beneficial. Lastly, for patients with advanced disease severity, who are unable to optimally participate in moderate intensity aerobic and resistance ET, utilization of NMES should be considered as a bridge/compliment to traditional ET approaches in those patients with advanced disease severity and substantial functional deficits. As a patient in this category improves functionally, the NMES component may be weaned as moderate intensity aerobic and resistance ET are up-titrated.

It is important to consider compliance and long term adherence with the ET program. Most patients with LSHD will begin an ET program from a state of minimal to no physical activity. As such, initiating too high of an ET volume at the onset of an ET program, with multiple training components (i.e., aerobic, resistance, IMT simultaneously) , may have a detrimental effect on long term adherence. A pragmatic approach may, therefore, be optimal, where components of the ET program are added one at a time, perhaps at a volume below target levels. For example, in a patient with the LSHD– PH phenotype, advanced disease severity, a completely sedentary lifestyle and a significantly compromised functional capacity, beginning an ET program with moderate intensity aerobic ET only, three times per week, ≈30 minutes per session, may be prudent; ET volume and components can be up-titrated gradually, being mindful of the patient's response to the program. In addition, there is a rapidly growing recognition that the patient should be an active participant in his or her plan of care, which includes the development and evolution of an ET program.[59] Taking a conservative and engaging approach may help optimize long term ET adherence and success.

The Need for ET Research in the LSHD – PH Phenotype

Research specifically investigating the effect of ET in the LSHD – PH phenotype is lacking. Given the high prevalence of PH in patients with LSHD, particularly those diagnosed with HF, investigation into this area is warranted. Several possible research lines are included herein.

Better elucidating the effect of ET on pulmonary hemodynamics, as well as vessel wall characteristics, would be of value. Studies assessing the acute and chronic effects of ET on RV structure and function in patients with the LSHD – PH phenotype would also be of high importance, including different training paradigms (e.g., moderate intensity aerobic training vs.

HIIT). Moreover, given the unique pathophysiologic processes associated with HFrEF and HFpEF, separate analyses into the unique effects of ET are warranted.

The optimal approach to treating the LSHD – PH phenotype would be preventing its onset completely. Recently, Wan et al.[60] described pre-clinical diastolic dysfunction, a phenomenon that precedes HF. In an associated editorial, Pressler et al.[61] proposed ET as an intervention of choice for pre-clinical diastolic dysfunction; the authors of this review echo support for consideration of such an approach. Future research assessing the impact of primary prevention ET interventions as a means to reduce the risk of developing HF altogether in patients at high risk would be a worthwhile endeavor.

Conclusions

Clearly, ET is now recognized as a valuable medical intervention in virtually all patient populations, including those diagnosed with the LSHD – PH phenotype. Ideally, patients should fully participate in a comprehensive ET program, individually tailored to optimally improve physiologic function and clinical outcomes. It is, however, important to recognize that "something is better than nothing" and a primary goal, particularly at the onset, is to transition from a completely sedentary lifestyle to some level of routine physical activity that is sustainable over the long-term. Moderate intensity aerobic ET should be viewed as the primary ET intervention in the LSHD – PH phenotype. Resistance ET and IMT can further enhance functional improvements in patients who demonstrate the willingness to be compliant with a multi-pronged ET program. Finally, NMES can be a useful tool in more advanced disease. To optimize long-term adherence, patients should be engaged as active participants in developing and, over time, evolving the ET program.

Reference Manager

1. Guazzi M and Arena R. Pulmonary hypertension with left-sided heart disease. *Nat Rev Cardiol*. 2010;7:648-59.

2. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R and Lancellotti P. Pulmonary hypertension in valvular disease: a comprehensive review on pathophysiology to therapy from the HAVEC Group. *JACC Cardiovascular imaging*. 2015;8:83-99.

3. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Després J-P, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW and Turner MB. Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association. *Circulation*. 2014.

4. Dupuis J and Guazzi M. Pathophysiology and Clinical Relevance of Pulmonary Remodelling in Pulmonary Hypertension due to Left Heart Diseases. *Can J Cardiol*. 2015;31:416-429.

5. Sallis RE. Exercise is medicine and physicians need to prescribe it! *British journal of sports medicine*. 2009;43:3-4.

6. Smart N, Haluska B, Jeffriess L and Marwick TH. Exercise training in systolic and diastolic dysfunction: effects on cardiac function, functional capacity, and quality of life. *Am Heart J*. 2007;153:530-6.

7. Taylor RS, Davies EJ, Dalal HM, Davis R, Doherty P, Cooper C, Holland DJ, Jolly K and Smart NA. Effects of exercise training for heart failure with preserved ejection fraction: a systematic review and meta-analysis of comparative studies. *Int J Cardiol*. 2012;162:6-13.

8. Downing J and Balady GJ. The role of exercise training in heart failure. *J Am Coll Cardiol*. 2011;58:561-9.

9. Klempfner R, Kamerman T, Schwammenthal E, Nahshon A, Hay I, Goldenberg I, Dov F and Arad M. Efficacy of exercise training in symptomatic patients with hypertrophic cardiomyopathy: results of a structured exercise training program in a cardiac rehabilitation center. *Eur J Prev Cardiol*. 2015;22:13-9.

10. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K and Singh S. Exercise-based rehabilitation for heart failure. *The Cochrane database of systematic reviews*. 2014;4:CD003331.

11. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, Coke LA, Fleg JL, Forman DE, Gerber TC, Gulati M, Madan K, Rhodes J, Thompson PD, Williams MA, Assoc AH, Cardiology CC, Metab CNPA, Nursing CCS and Prevention CE. Exercise Standards for Testing and Training: A Scientific Statement From the American Heart Association. *Circulation*. 2013;128:873-934.

12. Abudiab MM, Redfield MM, Melenovsky V, Olson TP, Kass DA, Johnson BD and Borlaug BA. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2013;15:776-85.

13. Little WC and Borlaug BA. Exercise intolerance in heart failure with preserved ejection fraction: what does the heart have to do with it? *Circ Heart Fail*. 2015;8:233-5.

14. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee D, Earnest CP, Church TS, O'Keefe JH, Milan RV and Blair SN. Exercise and the Cardiovascular System: Clinical Science and Outcome. *Circulation Research*. 2015;117:207-219.

15. Arena R, Lavie CJ, Milani RV, Myers J and Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. *J Heart Lung Transplant*. 2010;29:159-73.

16. Adams V and Niebauer J. Reversing heart failure-associated pathophysiology with exercise: what actually improves and by how much? *Heart Fail Clin*. 2015;11:17-28.

17. Arena R, Cahalin LP, Borghi-Silva A and Phillips SA. Improving functional capacity in heart failure: the need for a multifaceted approach. *Curr Opin Cardiol*. 2014;29:467-74.

18. Guazzi M, Gomberg-Maitland M and Arena R. Pulmonary hypertension in heart failure with preserved ejection fraction. *J Heart Lung Transplant*. 2015;34:273-81.

19. Keteyian SJ. Exercise Training in Congestive Heart Failure: Risks and Benefits. *Prog Cardiovasc Dis*. 2011;53:419-428.

20. Pandey A, Parashar A, Kumbhani DJ, Agarwal S, Garg J, Kitzman D, Levine BD, Drazner M and Berry JD. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. *Circ Heart Fail*. 2015;8:33-40.

21. Smart NA, Haluska B, Jeffriess L and Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. *Congest Heart Fail*. 2012;18:295-301.

22. Fujimoto N, Prasad A, Hastings JL, Bhella PS, Shibata S, Palmer D and Levine BD. Cardiovascular effects of 1 year of progressive endurance exercise training in patients with heart failure with preserved ejection fraction. *Am Heart J*. 2012;164:869-77.

23. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, Binder L, Topper A, Lashki DJ, Schwarz S, Herrmann-Lingen C, Loffler M, Hasenfuss G, Halle M and Pieske B. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*. 2011;58:1780-91.

24. Johnson EJ, Dieter BP and Marsh SA. Evidence for distinct effects of exercise in different cardiac hypertrophic disorders. *Life Sci*. 2015;123C:100-106.

25. Vuckovic KM, Piano MR and Phillips SA. Effects of exercise interventions on peripheral vascular endothelial vasoreactivity in patients with heart failure with reduced ejection fraction. *Heart, lung & circulation*. 2013;22:328-40.

26. Kitzman DW, Brubaker PH, Herrington DM, Morgan TM, Stewart KP, Hundley WG, Abdelhamed A and Haykowsky MJ. Effect of endurance exercise training on endothelial

function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. *J Am Coll Cardiol*. 2013;62:584-92.

27. Angadi SS, Mookadam F, Lee CD, Tucker WJ, Haykowsky MJ and Gaesser GA. High-intensity interval training vs. moderate-intensity continuous exercise training in heart failure with preserved ejection fraction: A pilot study. *J Appl Physiol (1985)*. 2014:jap 00518 2014.

28. Arena R, Myers J, Forman DE, Lavie CJ and Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? *Heart Fail Rev*. 2013;18:95-105.

29. Lavie CJ, Arena R and Earnest CP. High-intensity interval training in patients with cardiovascular diseases and heart transplantation. *J Heart Lung Transplant*. 2013;32:1056-8.

30. Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, Tjonna AE, Helgerud J, Slordahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najjar SM, Ellingsen O and Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. *Circulation*. 2007;115:3086-94.

31. Pinkstaff SO. Much potential but many unanswered questions for high-intensity intermittent exercise training for patients with heart failure. *Heart Fail Clin*. 2015;11:133-48.

32. Stoylen A, Conraads V, Halle M, Linke A, Prescott E and Ellingsen O. Controlled study of myocardial recovery after interval training in heart failure: SMARTEX-HF--rationale and design. *Eur J Prev Cardiol*. 2012;19:813-21.

33. Mandic S, Myers J, Selig SE and Levinger I. Resistance versus aerobic exercise training in chronic heart failure. *Current heart failure reports*. 2012;9:57-64.

34. Braith RW and Beck DT. Resistance exercise: training adaptations and developing a safe exercise prescription. *Heart Fail Rev*. 2008;13:69-79.

35. Montemezzo D, Fregonezi GA, Pereira DA, Britto RR and Reid WD. Influence of inspiratory muscle weakness on inspiratory muscle training responses in chronic heart failure patients: a systematic review and meta-analysis. *Arch Phys Med Rehabil*. 2014;95:1398-407.

36. Chiappa GR, Roseguini BT, Vieira PJ, Alves CN, Tavares A, Winkelmann ER, Ferlin EL, Stein R and Ribeiro JP. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. *J Am Coll Cardiol*. 2008;51:1663-71.

37. Ribeiro JP, Chiappa GR, Neder JA and Frankenstein L. Respiratory muscle function and exercise intolerance in heart failure. *Current heart failure reports*. 2009;6:95-101.

38. Jaenisch RB, Hentschke VS, Quagliotto E, Cavinato PR, Schmeing LA, Xavier LL and Dal Lago P. Respiratory muscle training improves hemodynamics, autonomic function, baroreceptor sensitivity, and respiratory mechanics in rats with heart failure. *J Appl Physiol (1985)*. 2011;111:1664-70.

39. Arena R, Pinkstaff S, Wheeler E, Peberdy MA, Guazzi M and Myers J. Neuromuscular electrical stimulation and inspiratory muscle training as potential adjunctive rehabilitation options for patients with heart failure. *J Cardiopulm Rehabil Prev*. 2010;30:209-23.

40. Karavidas A, Driva M, Parissis JT, Farmakis D, Mantzaraki V, Varounis C, Paraskevaidis I, Ikonomidis I, Pirgakis V, Anastasiou-Nana M and Filippatos G. Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and

emotional status in heart failure patients with preserved left ventricular ejection fraction. *Am Heart J*. 2013;166:760-7.

41. Karavidas AI, Raisakis KG, Parissis JT, Tsekoura DK, Adamopoulos S, Korres DA, Farmakis D, Zacharoulis A, Fotiadis I, Matsakas E and Zacharoulis A. Functional electrical stimulation improves endothelial function and reduces peripheral immune responses in patients with chronic heart failure. *European journal of cardiovascular prevention and rehabilitation : official journal of the European Society of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology*. 2006;13:592-7.

42. Karavidas A, Parissis JT, Matzaraki V, Arapi S, Varounis C, Ikonomidis I, Grillias P, Paraskevaidis I, Pirgakis V, Filippatos G and Kremastinos DT. Functional electrical stimulation is more effective in severe symptomatic heart failure patients and improves their adherence to rehabilitation programs. *J Card Fail*. 2010;16:244-9.

43. Jurgens CY, Goodlin S, Dolansky M, Ahmed A, Fonarow GC, Boxer R, Arena R, Blank L, Buck HG, Cranmer K, Fleg JL, Lampert RJ, Lennie TA, Lindenfeld J, Pina IL, Semla TP, Trebbien P and Rich MW. Heart Failure Management in Skilled Nursing Facilities: A Scientific Statement From the American Heart Association and the Heart Failure Society of America. *Circ Heart Fail*. 2015.

44. Arena R, Cahalin LP, Borghi-Silva A and Myers J. The effect of exercise training on the pulmonary arterial system in patients with pulmonary hypertension. *Prog Cardiovasc Dis*. 2015;57:480-8.

45. Waxman AB. Exercise physiology and pulmonary arterial hypertension. *Prog Cardiovasc Dis*. 2012;55:172-9.

46. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordegraaf A and Bogaard HJ. The Effects of Exercise on Right Ventricular Contractility and Right Ventricular - Arterial Coupling in Pulmonary Hypertension. *Am J Respir Crit Care Med*. 2015.

47. La Gerche A and Claessen G. Is Exercise Good for the Right Ventricle? Concepts for Health and Disease. *Can J Cardiol*. 2015;31:502-508.

48. La Gerche A, Burns AT, Mooney DJ, Inder WJ, Taylor AJ, Bogaert J, Macisaac AI, Heidbuchel H and Prior DL. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J*. 2012;33:998-1006.

49. La Gerche A, Heidbuchel H, Burns AT, Mooney DJ, Taylor AJ, Pfluger HB, Inder WJ, Macisaac AI and Prior DL. Disproportionate exercise load and remodeling of the athlete's right ventricle. *Med Sci Sports Exerc*. 2011;43:974-81.

50. O'Keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel RA and McCullough PA. Potential adverse cardiovascular effects from excessive endurance exercise. *Mayo Clin Proc*. 2012;87:587-95.

51. Keteyian SJ, Pina IL, Hibner BA and Fleg JL. Clinical role of exercise training in the management of patients with chronic heart failure. *J Cardiopulm Rehabil Prev*. 2010;30:67-76.

52. Williams MA and Pozehl B. Reasonable expectations: how much aerobic capacity, muscle strength, and quality of life can improve with exercise training in heart failure. *Heart Fail Clin*. 2015;11:37-57.

53. Cahalin LP, Arena R, Guazzi M, Myers J, Cipriano G, Chiappa G, Lavie CJ and Forman DE. Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes. *Expert review of cardiovascular therapy*. 2013;11:161-77.

54. Cahalin LP and Arena RA. Breathing exercises and inspiratory muscle training in heart failure. *Heart Fail Clin*. 2015;11:149-72.

55. Smart NA, Giallauria F and Dieberg G. Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *Int J Cardiol*. 2013;167:1502-7.

56. Smart NA, Dieberg G and Giallauria F. Functional electrical stimulation for chronic heart failure: a meta-analysis. *Int J Cardiol*. 2013;167:80-6.

57. Arena R. Exercise testing and training in chronic lung disease and pulmonary arterial hypertension. *Prog Cardiovasc Dis*. 2011;53:454-63.

58. Keteyian SJ, Leifer ES, Houston-Miller N, Kraus WE, Brawner CA, O'Connor CM, Whellan DJ, Cooper LS, Fleg JL, Kitzman DW, Cohen-Solal A, Blumenthal JA, Rendall DS and Piña IL. Relation Between Volume of Exercise and Clinical Outcomes in Patients With Heart Failure. *J Am Coll Cardiol*. 2012;60:1899-1905.

59. Ekman I, Wolf A, Olsson LE, Taft C, Dudas K, Schaufelberger M and Swedberg K. Effects of person-centred care in patients with chronic heart failure: the PCC-HF study. *Eur Heart J*. 2012;33:1112-9.

60. Wan S-H, Vogel MW and Chen HH. Pre-Clinical Diastolic Dysfunction. *J Am Coll Cardiol*. 2014;63:407-416.

61. Pressler A, Schwarz S, Christle J, Heinrich C, Edelmann F and Halle M. The Best Treatment Approach to Pre-Clinical Diastolic Dysfunction?: Think About Exercise Training! *J Am Coll Cardiol*. 2014;64:529-530.

Table 1: Exercise Training Program Recommendations

Adapted from: Arena R. Exercise testing and training in chronic lung disease and pulmonary arterial hypertension. *ProgCardiovasc Dis*. 2011 May-Jun;53(6):454-63 (Table 3).

Exercise Training Approach	**General Prescription Guidelines**	**Training Modes**
Aerobic: Moderate Intensity	• 3-7 days/week • 30-60 minutes/day (accumulated or continuous) • 50-85% of maximal aerobic capacity	• Walking/treadmill • Lower extremity ergometer • Elliptical • Combination of above
Resistance: Moderate Intensity	• 2-3 days/week • 1 set • 10-15 repetitions per set • 8-10 exercises; preferably multi-joint (e.g., bench press, hip sled, etc.) • Alternate upper and lower body exercise	• Cable weight systems • Free weights • Bands
Inspiratory Muscle	• 1-2 times/day • 15-30 minutes per session • 3-7 days/per week • ≥30% of maximal inspiratory pressure	• Handheld, threshold load trainer
Neuromuscular electrical stimulation	• Electrical frequency: 10-50 Hz • Pulse duration: 200-700 μseconds • On cycle: 2-10 seconds • Off cycle: 4-50 seconds • Intensity: visibly strong muscle contraction to maximal tolerance • 1-2 times/day • 30-60 minutes/session • 3-7 days/week • Electrical pads on bilateral quadriceps, calf and possibly hamstring muscles	• Handheld battery operated units

Figure 1: Comparison between normal and abnormal pulmonary arterial vessel response to exercise: implications for cardiac output with an acute exercise stimulus and right ventricular function with chronic exercise