Exercise intolerance in pulmonary hypertension: mechanism, evaluation and clinical implications

Abraham Samuel Babu[1], Ross Arena[2], Jonathan Myers[3], Ramachandran Padmakumar[4], Arun G. Maiya[5], Lawrence P. Cahalin[6], Aaron B. Waxman[7], Carl J. Lavie[8]

1. Department of Physiotherapy, School of Allied Health Sciences, Manipal University, Manipal – 576104, Karnataka, India
2. of Physical Therapy and Department of Kinesiology and Nutrition, University of Illinois at Chicago, Chicago, USA
3. Veterans Affairs Health Center / Stanford University, Palo Alto, California, USA
4. Department of Cardiology, Kasturba Medical College, Manipal University, Manipal – 576104, Karnataka, India
5. Department of Physiotherapy, School of Allied Health Sciences, Manipal University, Manipal – 576104, Karnataka, India
6. Department of Physical Therapy, Millers School of Medicine, Florida, USA
7. Pulmonary Vascular Disease Program, Director - Dyspnea and Performance Evaluation Center, Pulmonary Critical Care Medicine, Cardiovascular Medicine, Brigham and Women's Hospital, Associate Professor of Medicine, Harvard Medical School, 75 Francis Street, PBB CA-3, Boston, MA 02115
8. Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-The University of Queensland School of Medicine, New Orleans, USA

Address for correspondence:
Abraham Samuel Babu, Department of Physiotherapy, School of Allied Health Sciences, Manipal University, Manipal – 576104, Karnataka, India, Email: abrahambabu@gmail.com

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Abstract:

Introduction: Exercise intolerance in pulmonary hypertension (PH) is a major factor affecting activities of daily living and quality of life. Evaluation strategies (i.e., non-invasive and invasive tests) are integral to providing a comprehensive assessment of clinical and functional status. Despite a growing body of literature on the clinical consequences of PH, there are limited studies discussing the contribution of various physiological systems to exercise intolerance in this patient population. **Areas covered:** This review, through a search of various databases, describes the physiological basis for exercise intolerance across the various PH etiologies, highlights the various exercise evaluation methods and discusses the rationale for exercise training amongst those diagnosed with PH. **Expert commentary:** With the growing importance of evaluating exercise capacity in PH (class 1, Level C recommendation), understanding why exercise performance is altered in PH is crucial. Thus, the further study is required for better quality evidence in this area.

Keywords: Exercise, Pulmonary hypertension, Exercise capacity, Cardiopulmonary exercise testing

1. Introduction

Pulmonary hypertension (PH) is a result of progressive pathophysiologic remodeling in the pulmonary arterial (PA) system occurring from a variety of causes affecting the entire pulmonary vascular bed.[1,2] It has been defined by haemodynamic measures as pre-capillary and post-capillary PH.[3] However, based on the recent definition of the 5th World Symposium on Pulmonary Hypertension Symposium at Nice, France in 2013 PH is divided into five distinct

groups which are pulmonary arterial hypertension, PH due to left heart disease, PH due to lung disease, chronic thromboembolic PH and PH with unclear or multifactorial mechanisms.[1]

Reduced endurance or exercise capacity is a hallmark feature of PH. As per the recent guidelines, the evaluation of exercise capacity is an important aspect of the clinical evaluation for PH. In this regard, aerobic exercise testing, a universal marker of cardiovascular (CV), pulmonary and muscular health, clearly portends clinically important information relative to prognosis, functional capacity, and physiologic contributors to abnormal exertional symptoms.[4-7]

This paper will highlight the mechanisms of exercise intolerance in patients with PH and will describe the current methods used to evaluate exercise capacity in patients with PH. We will also discuss considerations for exercise prescription in this patient population.

2. Mechanisms for exercise limitations in PH:

Factors limiting exercise are influenced by the underlying pathophysiology of PH. Identification of these factors provides important objective measurements required for the planning and structuring of exercise-based interventions. The normal response to exercise in a healthy individual involves major adaptations on the CV, pulmonary and musculoskeletal systems. With regard to the pulmonary vasculature, in normal individuals, there is an immediate response to the increased cardiac output (CO) (i.e., during exercise) without elevating PA pressure (PAP) due to the high compliance of the PA vessel bed.[8] This high compliance of the pulmonary circuit facilitates the ability to accommodate rapid increases in circulating blood volume.

2.1 Pulmonary circulation

Changes in pulmonary vascular resistance (PVR) have been explained by two physiological, flow related mechanisms (i.e., steady flow and pulsatile flow).[9] Steady flow hemodynamics is a simplified model that calculates resistance by a single point pressure difference-flow ratio, while pulsatile flow haemodynamics takes into consideration the variation in PA pulse pressure with the systolic and diastolic phases of the cardiac cycle. The total PVR is the ratio between the mean pressure drop across the vascular system [which is equal to the mean PA pressure (mPAP) minus the left atrial (LA) pressure (LAP) or pulmonary capillary wedge pressure (PCWP)] and mean flow into the system [which is equal to the CO(Q)]. Vascular resistance is dependent on the properties of the vessel and its contained fluid, with a pattern of unidirectional and constant blood flow. In PH, exercise is limited, in part by the inability of the right ventricle to sufficiently increase pulmonary blood flow due to increased PVR

$$PVR = mPAP\text{-}mLAP/Qp \qquad \text{(Equation 1)}$$

where mLAP is the mean LAP. In addition, a minimal alteration in the radius of the vessel alters the resistance of the pulmonary circulation, resulting in an almost four fold increase in PVR.[10]

Understanding the relation between Q and oxygen uptake (VO_2) is explained by the Fick equation which can be rearranged to illustrate the relationship of oxygen uptake to CO:

$$VO_2 = Qp \times (C_aO_2 - C_vO_2) \qquad \text{(Equation 2)}$$

where VO_2 is oxygen uptake, Qp is cardiac output and C_aO_2-C_vO_2 is the arteriovenous oxygen content difference. From both of these concepts, it is clear that any factor that alters Qp can have an effect on PVR which will further affect Qp resulting in an altered VO_2.

Along with these changes, the pressure-volume relationship seen in the pulmonary circulation is of great significance to understanding the exercise limitations. Various models have shown a pulmonary vascular distensability of 2%/mmHg decreases mPAP at high Qp.[11]

However, changes in distensibility to 0.1%/mmHg, greatly increase the mPAPA thereby limiting exercise.

2.1.1 Exercise induced pulmonary hypertension:

Exercise induced PH (EiPH) is seen to occur when apparently normal individuals are exercised. This feature occurs as a result of an increase in PVR or due to an excessive left atrial pressure in left heart disease.[12] Increase in PAP to >30mmHg at a Qp<10L/min in response to exercise has been found to be associated with dyspnea and fatigue among individuals at risk of developing PH.[11] A recent paper found that a mean PAP>30mmHg along with a total pulmonary resistance of >3mmHg/min/L had higher specificity and sensitivity (1.0 and 0.93) than the previously described criteria >30mmHg (0.77 and 0.98).[12] The entity of EiPH can limit exercise through the pulmonary vascular response in early stages. Further discussion in this area is beyond the scope of this review paper and the readers can refer to key papers in this area.[11,13]

2.2 Right and Left ventricle

The right ventricle (RV) is a thin walled, crescent shaped chamber that is sensitive to afterload.[14,15] RV function is regulated through the Frank-Starling mechanism and the autonomic nervous system.[16] Therefore, the RV adapts better to volume overload than pressure overload.[17] However, as the load on the RV continues to rise, it fails to preserve systolic function which in turn results in increased dimensions of the RV thereby altering diastolic function and limiting exercise capacity as a result of uncoupling of the RV-PA unit.[18] The uncoupling between the RV and pulmonary vasculature results in a triad of changes viz., RV systolic dysfunction, increase size of the RV and an alteration in the shape of the RV.[19] This alteration in shape of the RV results in compression of the LV as a result of the leftward shift in the interventricular septum

and also affects the reduces the LV distensability by the increase in constrain through the pericardium.[17] Impaired diastolic function of the RV limits RV filling which results in an increase in the RV diastolic pressure. The severity of changes are related to the degree of uncoupling that occurs. As compensatory RV hypertrophy progresses, there are further increases in the degree of uncoupling.[19] This greatly affects the contractile ability of the RV to increase during exercise in response to an increased RV afterload (i.e., failure of the RV exertional contractile reserve, which is measured from rest to exercise).[20] This change would indicate that patients with PH do not have the ability to increase their RV exertional contractile reserve, thus limiting exercise. In addition, due to the altered LV geometry, despite a rise in heart rate during exercise, the stroke volume fails to rise sufficiently during exercise. This bi-ventricular interaction, along with various other factors contributes to limited exercise performance.

2.3 Respiratory function

Patients with PH typically reveal a distinct pattern in response to exercise. There is typically a higher peak heart rate and impaired heart rate recovery.[21] In addition, as mentioned earlier, stroke volume augmentation is impaired, and both peak VO_2 and the O_2-pulse are reduced (Box 1). There is a reduction in ventilatory efficiency with a reduced VO_2 at the anaerobic threshold (AT) and an increased minute ventilation/carbon dioxide production (VE/VCO_2) slope due in part to impaired blood flow and reduced pulmonary vascular perfusion leading to increased dead space ventilation (VD).[6,21,22] To compensate for increased VD, the patient's ventilatory requirement must increase. The inability to increase Qp impairs oxygen delivery in response to exercise, leading to a low work rate and relative acidosis [as a result of reduced ventilatory efficiency and decreased partial pressure of end-tidal CO_2 ($P_{ET}CO2$)] and, in some cases exercise-induced hypoxemia, stimulating the ventilatory drive. The decrease in

ventilatory efficiency results in an increase in VE/VCO_2 and a decrease in $P_{ET}CO2$ at the AT. Both VE/VCO_2 and $P_{ET}CO2$ at the AT (measures of increased VD/VT), as well as peak VO_2 and peak O_2-pulse (measures of decreased Q), correlate with the severity of disease in PH patients.[21] Abnormalities in diffusion capacity have also been thought to be due to reduced diameters of the pulmonary vessels causing a disproportionate reduction in diffusion across the membrane when compared to the capillary blood volume.[22] In addition hypoxemic vasoconstriction and can further limit exercise performance across the various groups of PH in which hypoxemia is a major finding.[23]

2.4 Peripheral muscles

In addition, peripheral muscle contributes greatly to the exercise limitation seen in patients with PH. This is thought to be due to the circulatory changes leading to poor peripheral oxygen delivery resulting in significant exercise limitation in proportion to the disease progression.[24] Recent muscle biopsy studies have shown a decrease in the ratio of type I to type II fibers along with reduction in cross sectional area of the type I fibers.[25] These changes in quadriceps muscle function have resulted in a decreased force generation capacity when compared with healthy controls.[26] These changes could contribute to a greater lactic acid build up at lower intensities of exercise cause early peripheral muscle fatigue that contributes to the exercise limitation in PH.[22] In patients with HF, the reduced circulation results in activation of mechanoreceptors in the muscle causing an abnormal metaboreflex or chemoreflex which in turn contributes to the increased ventilatory demand. In PH however, there are limited data assessing the contribution of the metaboreflex to exercise limitation. Along with these peripheral muscle changes, reductions in diaphragmatic strength by 20-25% as determined from maximal inspiratory pressure have been observed.[27,28] Along with this, there are changes in muscle fiber

properties like cross sectional area, contractility, capillarity and oxidative capacity seen in patients with PH. [29]

The next few sections will review the contribution to exercise limitation from the various physiological systems for the different groups of PH described at the recent Niece World Pulmonary Hypertension Symposium.[1]

3. Exercise limitation in various etiological groups of pulmonary hypertension

3.1 Group 1(Pulmonary arterial hypertension)

Exercise limitation seen among those with idiopathic pulmonary arterial hypertension (iPAH) were initially reported by Sun et al.22[19] They postulated two pathways underlying the degree of exercise limitation associated with the increase in PVR: 1) increased ventilatory requirement and 2) impaired muscle contraction.

The alterations in PVR that lead to poor recruitment of the pulmonary vascular bed causes a ventilation perfusion mismatch leading to an increase in the dead space to tidal volume ratio, leading to an increase in the ventilatory requirement.[22] In addition, contributions from central haemodynamic changes (i.e., reduced RV contractility and SV) further limit exercise performance in these patients.[30] The insufficient fall in PVR during exercise places a greater load on the RV which eventually results in RV dysfunction as a result of the altered length-tension relation due to the dilated RV.

An important role of the peripheral muscles in exercise limitation has been demonstrated in patients with iPAH.[29,31] Contribution from weakness of the respiratory musculature has also been studied by Meyer et al., where they found reductions in both inspiratory and expiratory muscle function among those with iPAH.[32] They described the following potential mechanisms

inferred from studies in HF and COPD: 1) Impaired muscle perfusion; 2) Reduction in number and size of mitochondria; and 3) Decreased oxidative enzymes. In addition, they suggested a role of electrolyte imbalances and steroid therapy as potential mechanisms worsening muscle weakness. The existing peripheral dysfunction could also be the result of a severely impaired extraction of O_2 which is reflected by an impaired systemic oxygen extraction ratio in PH compared to systolic HF (0.619 versus 0.744; $p<0.05$).[24] This is similar to the altered ergoreflex or metabo-reflex described earlier.

In addition to these mechanisms, impaired autonomic regulation as identified through impaired heart rate recovery (HRR) following either cardiopulmonary exercise testing (CPX) or the six minute walk test (6MWT) has been seen in iPAH.[33,34] This parameter was shown to be a strong predictor of clinical worsening in iPAH.[34]

Apart from these mechanisms, the role of micro RNAs (especially microRNA-126) have recently received a great deal of attention in identifying exercise limitations and the pathophysiology of PH. MicroRNA-126 is an endothelial specific microRNA that modulates angiogenesis and maintains vascular integrity.[35] A recent study found that impaired skeletal muscle perfusion and altered angiogenesis – both factors contributing to the peripheral muscle dysfunctions in PH, are the result of a decreased microRNA-126 expression.[36] In addition to the progression of the peripheral muscle dysfunction, alteration in the structure of the microRNA-126 and microRNA-130/301 have been identified as a regulator of cellular proliferation and the progression of PAH.[37] These genetic dysfunctions further contribute to exercise limitation in PAH.

3.2 Group 2 (PH due to left heart disease)

Heart failure with either reduced (HFrEF) or preserved ejection fraction (HFpEF) leads to limitations to exercise through both central and peripheral mechanisms; these limitations vary in severity and relate to the severity of pathophysiology present in this patient population.[38] The co-existence of PH in these patients will further augment the exercise limitations. HFrEF produces limitations to exercise performance through the interaction of various systems. These mechanisms include a reduction in cardiac output primarily, but impaired ventilation, skeletal muscle function, endothelial function and the neurohumoral system contribute to the poor exercise performance in HFrEF.[39,40] The impact of HFrEF on PAP is a gradual process due to the prolonged elevation of the PCWP.[41] There exists a controversy regarding the need for identifying pre- or post-capillary PH in left heart disease.[42] Nevertheless, it is important to identify PH in this group as the resulting RV dysfunction from PH alters prognosis in these patients.[43] Further discussion with respect to HFrEF is beyond the scope of this paper.

HFpEF contributes greatly to the development of PH. A recent review by Guazzi et al., highlighted the various limitations in HFpEF and elucidated the factors leading to PH.[44] An interplay between vascular dysfunction (wall stiffening and abnormal vasorelaxation) and cardiac changes (hypertrophy, fibrosis and poor coronary reserve) results in an increased load on the LV and raises the end-diastolic pressure–volume relationship. Together, these changes underlie an increased LA upstream pressure causing an elevation in pulmonary venous and pulmonary arterial pressure. The chronic increase in LAP eventually can lead to remodeling of the pulmonary arterial bed, decreased compliance of the pulmonary arterial bed, and an increase in the oscillatory load on the RV.[45] This vascular-ventricular uncoupling results in a reduction in peak VO_2 by altering both Q and PVR (equations 1, 2 and 3). The increased left atrial (LA) pressure results in alveolar-capillary remodeling, which may not be reversible.[44] At peak exercise

in HFpEF, there is an abnormal rise in RAP and PAP (**Table 1**). In addition, peripheral mechanisms (viz., muscle fiber changes, reduced mitochondria and oxidative metabolism) will add to exercise intolerance in this group of patients.[38]

Apart from HFpEF, valvular disease contributes greatly to the development of PH in this group as well. Regardless of the valvular lesion (i.e., regurgitation or stenosis) in either the aortic and mitral valves), the consequence is an overloaded LA from either an increased LV end diastolic pressure or LA volume overload.[46] The resulting increased LAP starts the PH cascade by reducing LA compliance and increasing the backward pressure on the pulmonary veins resulting in vascular changes in the pulmonary veins and arteries. This causes a rise in PVR which in turn raises the PAP resulting in PH. Early studies have shown that individuals with aortic and mitral valve disease have high PVR and PAP.[47] Yet, despite the effectiveness of valve replacement, abnormal LV filling pressures continue and along with chronic changes in the pulmonary vascular bed.

CPX can help to identify these limitations in HF. The recent joint statement by the European Association for Cardiovascular Prevention and Rehabilitation and the American Heart Association recommends using several key exercise testing parameters to assess prognosis and assist in gauging disease severity [i.e., VE/VCO_2 slope, peak VO_2, exercise oscillatory ventilation and the $P_{ET}CO_2$] in a color-coded algorithm.[48]

3.3 Group 3 (PH due to lung disease and/or hypoxia)

Patients with pulmonary disease tend to have severe pulmonary mechanical and peripheral limitations, in addition to the pulmonary vascular and cardiac limitations. Obstructive and restrictive lung diseases greatly affect the biomechanical structure of the thorax thereby affecting ventilation and pulmonary function, both at rest and during exercise. In addition,

skeletal changes in the thorax contribute to abnormal biomechanical function.[49] The decreased lung volumes in diffuse parenchymal lung disease result in chronic alveolar hypoxia which causes hypoxia-induced vasoconstriction, further contributing to the increased pulmonary vascular resistance.[50] The resulting abnormal ventilation-perfusion (V/Q) mismatch, along with the accumulation of lactic acid in the exercising muscle is responsible for the increased production of carbon dioxide (VCO_2) during exercise. Thus, a major contributing factor to the high PAP is the high PVR which results from a variety of factors, including hypoxia-induced vasoconstriction, co-existing LV diastolic dysfunction, remodeling of the vascular bed, altered gas exchange, biomechanical abnormalities (e.g., hyperinflation and heightened intra-thoracic pressures) and musculoskeletal abnormalities.[10,50-53] In addition to these factors, the role of mitochondrial dysfunction and alterations in arterio-venous oxygen difference, both of which negatively impact peripheral O_2 uptake, further contribute to exercise limitations.[54] The disease process causes significant exercise limitation due to reductions in forced expiratory volume in one second (FEV_1) and tidal volume, in addition to an increase in end expiratory lung volume during exercise resulting in dynamic hyperinflation.[10,52]

In patients with ILD, ventilatory abnormalities in $P_{ET}CO_2$ and VE/VCO_2 ratios are suggestive of PH.[55] These changes result in an alteration in the matching of ventilation and perfusion in the lungs which is reflected through CPX as abnormal changes in ventilatory efficiency, including: 1) a reduction in $P_{ET}CO_2$ at rest and during exercise; 2) An increase in the VE/VCO_2 ratio or slope; and 3) an increase in the Vd/Vt ratio.[49,55] These changes are reflective of limitations from two main sources viz., mechanical factors and pulmonary vascular bed contributions. In addition, the significant contribution from the peripheral muscles and diaphragm as a result of the central disease process cannot be underestimated.[51] Along with

abnormalities in $P_{ET}CO_2$, the change in this, i.e., " $P_{ET}CO_2$ from rest to AT, has also been shown to have importance in identifying individuals with pulmonary vasculopathy.[56,57] In addition, VE/VCO2@AT is another parameter which is very closely related to the presence of PH, especially in patients with ILD.[58]

In addition to these abnormalities, both these groups of patients also present with peripheral muscle dysfunction including diminished muscle strength, atrophy, mitochondrial dysfunction, poor oxidative capacity and a shift in muscle fiber types (type II to type I).[49, 51,52] Changes in diaphragm structure and function further contributes to the respiratory changes seen in both obstructive and restrictive lung diseases. In obstructive diseases, there is a change in position of the diaphragm adversely affects respiratory muscle strength and exercise tolerance.[59] In those with restrictive lung diseases, along with the diaphragmatic dysfunctions, hypoxemic dysfunctions are a major concern in these patients.[60] Despite these differences, a recent study did not find any disease specific difference in diaphragm muscle activity between these two groups (i.e., obstructive and restrictive).[61]

These changes vary considerably from patients with group 1 PH particularly with respect to the contributions of the pulmonary system and the greater peripheral dysfunction that is common in those with chronic lung disease. However, there is a great deal of similarity with regard to haemodynamic responses to exercise among all PH categories. Distinguishing between these systemic contributions is indeed a challenge and opens up avenues for investigations using both non-invasive and invasive CPX to identify exercise limiting factors and also to assess the response to various therapeutic interventions. Thus, patients with pulmonary disease have significant limitations in exercise performance and these limitations are increased further in the presence of PH.

3.4 Group 4 (Chronic thromboembolic pulmonary hypertension)

Chronic thromboembolic pulmonary hypertension (CTEPH) results from incomplete resolution of the vascular obstruction associated with pulmonary thromboembolism resulting in increased PVR and high PAP.[62] V/Q mismatch as a result of altered perfusion causes an increase in dead space ventilation thereby altering the VD/Vt ratio. In addition, the RV plays an important role contributing to poor exercise tolerance. This could be due to a poor RV adaptation to exercise, causing a reduced RV stroke volume which is more common in the elderly given that CTEPH occurs more often with ageing.[63]

It has been reported that following endarterectomy, patients improve their exercise performance and quality of life.[64] However, this improvement in peakVO2 did not demonstrate statistical significance in correlation with the PVR ($r = -0.41$, $p =$ statistically significant correlation observed between the Ve/VCO2 slope and PVR ($r = 0.54$, $p < 0.05$).. Desp to persist in many patients.[65] Even though RV ejection fraction is preserved, the mechanism through which this is obtained (i.e., increase in both RV end diastolic and systolic volumes), is abnormal.[66] This brings to light the high dependence of the RV on the Frank Starling mechanism. Apart from the RV, altered pulmonary vascular compliance has also been reported to contribute to exercise limitations in these patients.[66] In addition, the presence of chronotropic incompetence is further thought to limit exercise performance in patients who have undergone endarterectomy.

3.5 Group 5 (PH with unclear multifactorial mechanisms)

Specific exercise limitations in this group are not as clear given that there are numerous underlying causes for PH. Unfortunately, due to the heterogeneity in causes leading to PH, there is very limited literature available on the exercise limitations seen in this group. This group of patients warrants more research in order to help ascertain the specific exercise limitations seen with various underlying causes viz., blood disorders.

Sickle cell disease causes chronic vasculopathy that results in 3-7% of these patients going on to develop PH.[67,68] In addition, abnormal pulmonary function is common, characterized by a restrictive pattern and abnormal diffusion capacity.[69] The changes to the blood cells and ventilatory system can result in poor oxygen transport thereby limiting exercise performance. This has been supported by studies which have demonstrated poor functional capacity, expressed as six minute walk distance (6MWD) and peak VO_2.[70] Other conditions such as chronic myeloproliferative disorders also predispose a person to PH either from CTEPH or through pre-capillary mechanisms. The limitations to exercise related to the pathophysiology of CTEPH has been reviewed above.

The above sections elucidate the important contribution of various physiological systems to exercise intolerance (**Table 2**). However, identifying these limitations requires evaluation of these physiological systems during stress or exercise. The subsequent sections describe methods to evaluate exercise capacity and the response of the pulmonary system to exercise in addition to the implications of exercise related variables in the clinical assessment and prognosis of patients with PH.

4. Methods for evaluating exercise intolerance in PH

4.1 Cardiopulmonary exercise testing (CPX)

CPX, merging standard clinical exercise testing techniques with breath by breath gas analysis, is the gold standard for the evaluation of aerobic fitness. This method allows for a much more precise quantification of aerobic capacity via peak VO_2 and subject effort via the peak respiratory exchange ratio (RER). Peak RER is the "gold standard" criterion to determine subject effort, with a value e 1.10 generally indicating a maximal test.[71,72] CPX in high risk groups such as PAH has shown to be safe in both adults and children,[22,73,74] and has been recommended for the screening and prognostication of patients with PH.[3] A recent evidence based review has suggested the use of CPX for diagnostic evaluation (Level B, Class IIa), prognostication (Level B, Class IIb) and determining therapeutic efficiency (Level C, Class IIb).[75]

Ventilatory inefficiency, commonly quantified by the VE/VCO_2 slope or ratio and $P_{ET}CO_2$, are only obtainable through ventilatory expired gas analysis and these responses have particular value in patients with PAH.[1821] The likelihood of PAH during CPX while evaluating persons with dyspnea was demonstrated using key CPX variables such as $P_{ET}CO_2$ and the VE/VCO_2 ratio at the ventilatory threshold (VT).[50] Patients with $P_{ET}CO_2$ values of > 36 mmHg and VE/VCO_2 ratios at the VT < 30 are unlikely to have PAH, while values below and above 36 mmHg and 30 increase the likelihood of PAH. A prognostic algorithm based on CPX variables has been suggested in the recent AHA/ESC guidelines and has important clinical applications for patients with PAH.[48] Recently a novel scoring system, the 4-parameter-CPET (4-P-CPET) score has been developed to detect CTEPH, demonstrating a sensitivity and specificity of 83.3% and 92.2%, respectively.[76] This scoring system utilizes the VE/VCO_2 slope, the alveolar-arterial oxygen gradient [$P(A\text{-}a)O_2$], the arterial to *end-tidal* CO_2 gradient [$P(c\text{-}ET)CO_2$] and $P_{ET}CO_2$. Therefore, in addition to identifying the exercise limiting factors, information from CPX also

aids in prognosis, diagnosis and gauging disease severity in patients with PH. The prognosis associated with various CPX responses is summarized in **Table 3**.

Thus, aerobic exercise testing provides a means to: 1) Objectively quantify the magnitude of functional limitation/disability present as a consequence of the disease process and concomitant deconditioning; 2) Provide a metric for quantifying disease severity and prognosis; 3) Assess the response to clinical interventions through serial testing; and 4) Develop an individually tailored exercise training program within safe physiologic parameters.

4.2 Sub-maximal tests

Submaximal functional tests have also proven useful and are appropriate in situations where CPX is not available. These tests typically evaluate a patient's walking capacity, performed in a hallway. They are advantageous in that they are simple to perform and require a lower degree of supervision compared to clinical exercise testing. Of the various submaximal tests, the six minute walk test (6MWT) has been the most widely used among patients with various cardiovascular and pulmonary conditions, including PAH.

The ATS has provided detailed guidelines on the proper procedure for the 6MWT in order to ensure reliability.[77] Recently, an evidence-based review on the validity and reliability of the 6MWT was published by the European Respiratory Society and ATS.[78] This statement identified the minimal clinically important difference (MCID) to be in the range of 25-33m for patients with chronic respiratory diseases. In PH, Mathai and colleagues have suggested a similar MCID (33m) as reported in the recent ERS-ATS statement.[79]

Distance walked during a submaximal test is a different metric than peak VO_2. Studies have reported relatively modest to strong correlation coefficients between 6MWT performance

and peak VO_2 (ranging between 0.40 and 0.80) including studies assessing patients with PAH.[80-82] Studies have also developed equations using the 6MWT to predict peak VO_2 in both HF and COPD cohorts, and the estimated values for peak VO_2 have been demonstrated to be reasonable approximations of maximal exercise capacity.[83-85]

Despite the wide use of the test in PH, there are certain limitations that need to be considered. Methodological variation including the setting of the test (indoor versus outdoor), length and shape of the track, and encouragement and instructions have been shown to alter the distance walked.[78] There is also a demonstrable ceiling effect when used among healthier age groups or higher functional levels. In addition, variations with populations, height, weight, age and sex need to be considered when interpreting the 6MWT.[21] Despite these limitations, the 6MWT is a simple and inexpensive test that is responsive to interventions and can be used as a surrogate marker to assess the functional capacity of patients with PAH when resources are limited. Apart from the 6MWT, significant associations have been reported between the step test and various prognostic parameters (i.e., WHO functional class, brain natriuretic peptide, RAP, PASP and MPAP) in PAH.[86]

4.3 Exercise echocardiography

Including echocardiography in conjunction with physical exertion has become an increasingly popular method for evaluating cardiac function during clinical exercise testing. Most commonly the echocardiographic measurements are taken either immediate post-treadmill testing or using a recumbent or semi-recumbent bicycle to allow for continuous, real-time imaging.[87] Four chamber apical views are commonly used to assess both LV and RV function, wall motion abnormalities and regurgitation (both mitral and tricuspid). Though it is challenging

and requires expertise, this technique has found wide application in the assessment of cardiovascular risk, PH, valvular diseases, HF and cardiomyopathies, among other indications.[88]

With regard to PAH, exercise echocardiography has been useful in identifying abnormal pulmonary vascular responses during exercise among those at risk for PAH.[88] Most measurements obtained from exercise echocardiography include right ventricular systolic pressure (RVSP), pulmonary artery systolic pressure (PASP), tricuspid annular plane systolic excursion (TAPSE) and peak tricuspid regurgitation (TR) velocity. PASP is determined using the standard modified Bernoulli equation:

$$PASP = [4(TR\ velocity)^2] + RAP$$

An inadequate PASP rise (<30mmHg), during exercise has been demonstrated to predict poor prognosis and poor performance on the 6MWT.[89] A recent study found TAPSE and the tricuspid annular systolic velocity during bicycle ergometry reflected the RV response to exercise.[90] Recently, poor linearity in the relationship between oxygen consumption to work rate ($\dot{V}O_2/\dot{W}R$) obtained from CPX along with reduced peak TAPSE and an abnormally high PASP was studied in patients with HF to help in identifying those having a primary RV - pulmonary vascular uncoupling.[20] It was seen that PASP (OR 1.06; 95% CI: 1.01-1.11) and TAPSE (OR 0.88; 95% CI: 0.8-0.97) were the strongest predictors contributing to this flattening which was further accompanied by a reduced peak VO2 and an impaired ventilatory efficiency. This flattening suggests an abnormal pulmonary vascular response to exercise among a groups of individuals with RV-pulmonary vascular uncoupling; thus, making the relevance of exercise echocardiography in assessment of the pulmonary vascular response to exercise.

A major limitation to the use of exercise echocardiography relates to the timing and the available window. In cases where the echocardiographic parameters are obtained immediately

after peak exercise, there is a very small window available to view the changes in TR velocities with peak exercise.[6] In addition, underlying obstructive lung diseases and obese individuals make obtaining a good quality echocardiographic image difficult. The latter is a limitation even when continuous echocardiographic monitoring is performed in the left lateral position.

4.4 Invasive CPX[91]

Combining CPX with exercise hemodynamic measurements permits evaluation of pulmonary arterial and cardiac filling pressures during exercise in combination with objective metrics of health and fitness. Simultaneous CPX and exercise hemodynamic assessment is done with pulmonary artery and radial artery catheters, along with breath-by-breath analysis of respiratory gas exchange at rest and during a period of incremental exercise to exhaustion. This approach provides an assessment of exercise capacity, and defines the detailed contributions of any cardiac, pulmonary vascular, or metabolic limitations based on direct Fick principles.

Physiologic measurements of RA, RV and PAP are measured continuously using a hemodynamic monitoring system. In addition, mean end-expiratory values for RAP, RVP, PAP and PCWP are obtained every minute during the study, in addition to systemic arterial pressure (BP) obtained with a radial artery catheter. These are further supplemented by mixed venous and peripheral arterial blood gas and lactate concentrations in arterial blood. With the evolution of a protocol for invasive CPX, there will hopefully now be standards which can be followed which will help in consistency across all centers performing invasive CPX.[92]

Data from studies using invasive CPX for the evaluation of unexplained dyspnea have, based on real time hemodynamic and exercise physiologic findings, been used to characterize the phenotype of individuals with exercise induced PH (EiPH).[91] These patients exhibit normal

mPAP at rest but develop PAH with exercise without evidence of diastolic dysfunction. Data suggest that patients with EiPH have significantly lower exercise capacity, higher peak mean PAP (18.0±2.5 at rest to 36.6±5.7 mm Hg), and a blunted decrease in PVR (223±82 at rest compared to 161±60 dynes.s.cm-5) with exercise. A comparison of the various physiological outcomes at peak exercise for a normal individual, one with mild resting PH and one with HFpEF is summarized in **Table 1**.

4.5 Inspiratory muscle testing

The contribution of inspiratory muscle weakness to exercise limitations, especially in patients with underlying lung disease, has been established.[29,32] The role of respiratory muscle weakness has also been demonstrated in PH. However, there is limited evidence regarding the extent to which it contributes to the exercise limitations in various groups of PH. From the existing studies illustrating the contribution of the respiratory musculature to exercise limitations, it is clear that the assessment of strength, endurance and fatigue of the respiratory muscles is a valuable pursuit.[93] Therefore, there is a need for more studies assessing respiratory muscle function in those with PH. Current recommendations for evaluating inspiratory muscle strength and endurance follow ATS and ERS guidelines and are widely used in patients with COPD.[93]Following the ATS/ERS guidelines is recommended until there can be larger cohorts assessing inspiratory muscle strength and endurance, highlighting the issues relating to feasibility and associated problems with the current recommendations.

5. Implications for exercise training:

From the above mentioned exercise limitations and the understanding of the pulmonary vascular response to exercise, it is reasonable to suggest that exercise training has the potential to

counteract many of the exercise limiting factors observed in PH. However, despite the strong physiological basis for recommending exercise training, there remains insufficient high quality evidence to strongly support or refute the use of exercise training as a part of a comprehensive care plan in patients with PH. Results from recent reviews and a meta-analysis have shown significant benefits with regard to exercise training on exercise capacity, quality of life and the pulmonary vascular system.[10,94-97] These similar findings were also observed in a recent clinical trial among patients with CTEPH.[98] In addition to these benefits, the use of both respiratory muscle and aerobic training have shown exercise to be cost effective in a European model.[99]

Moderate intensity exercise (e.g., 50-60% of VO_2 reserve) is a conservative approach to prescribing exercise training intensity in patients with PH. Resistance training will help further counteract skeletal muscle strength and endurance limitations that are common in patients with PH, adding to enhanced functional capacity and the ability to perform activities of daily living. Considering the involvement of the respiratory musculature in exercise limitations in PH, the role of inspiratory muscle training appears highly promising.[32] High intensity interval training has been used in patients with HF, with studies reporting both clinical and physiological benefits following this intervention.[100] However, a conservative approach to exercise training in patients with PH is currently recommended given the limited evidence regarding the safety and efficacy of higher intensity exercise training in this patient population. Even though aerobic training would likely be beneficial to all groups of PH, it is reasonable to recommend specific training programs according to the exercise-limiting factors seen across the various PH groups (**Table 4**). The effects of group-specific exercise interventions in PH should be studied in future clinical trials.

6. Future recommendations:

There remains a vast volume of work to be done on the study of exercise physiology in PH with respect to identification of mechanisms, imaging and long term implications. With regard to mechanisms, the rate of VO_2 increase to work rate, i.e., • VO_2/• WR slope, which is an indicator of CV efficiency that reflects aerobically generated ATP and exercise oscillatory ventilation have not been studied sufficiently in PH and will provide greater insight into the exercise limitations. The use of cardiac MRI to help better understand the RVs response to exercise may help uncover new mechanisms limiting and resulting in adaptation to exercise. Studies assessing the long term impact of these exercise limiting factors and how they are affected by exercise training will lead to better therapeutic choices in PH. Additional long term follow-up studies in PH are lacking and are needed to improve risk stratification.

7. Summary:

Exercise limitations in PH commonly include a combination of central and peripheral mechanisms. The synergistic contribution of these systems to the exercise limitation vary depending upon the etiology and severity of PH. Evaluating the influence of each physiologic component to the exercise limitation in a given patient is crucial to providing an exercise training program that will derive maximal benefits.

8. Expert commentary

Evaluation of exercise capacity has now gained an important place in the evaluation, risk stratification and prognostication for patients with PH and currently has a class 1, Level C recommendation.[3] Considering the current evidence based recommendation for evaluating

exercise capacity, it is imperative that there be an in-depth understanding to the mechanisms contributing to the limitations in exercise capacity. The contributions of the various physiological systems suggest that there is potential for reversibility of some of these dysfunctions – especially those observed in the peripheral muscles.[29] The potential reversibility has been observed in various clinical trials on exercise training in PH.[96,97] Despite the evidence available, the quality of studies are still of low methodological rigor which has resulted in a class IIa, Level B recommendations in the recent guidelines.[3]

9. Five-year view

Exercise limitations in PH are the result of dysfunctions from various physiological systems. Exercise testing has been used widely for the evlaution of these physiological dysfunctions. However, the evaluation of exercise limitations in PH still has a long way to go. Contributions of the autonomic system, inflammatory markers, endothelial dysfunctions and other cellular pathways that can influence exercise need to be evaluated. With the growing body of evidence studying exercise haemodynamics in PH, there is definitely going to be a greater understanding to the various central causes to exercise intolerance in PH.

Key Issues

- Exercise limitations in pulmonary hypertension are multi-factorial.
- Each clinical group of pulmonary hypertension has unique contributors to exercise limitations.
- Evaluation of these limitations can be done by various exercise testing methods (i.e., 6-minute walk test, cardiopulmonary exercise testing, exercise echocardiography and invasive cardiopulmonary exercise testing).
- Identification of exercise limitations is important for exercise training.

References

1. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62(25 Suppl):D34-41
2. Mocumbi AO, Thienemann F, Sliwa K. A global perspective on the epidemiology of pulmonary hypertension. Can J Cardiol. 2015;31:375-81
3. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, Simonneau G, Peacock A, Vonk Noordegraaf A, Beghetti M, Ghofrani A, Gomez Sanchez MA, Hansmann G, Klepetko W, Lancellotti P, Matucci M, McDonagh T, Pierard LA, Trindade PT, Zompatori M, Hoeper M; Authors/Task Force Members. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016 Jan 1;37(1):67-119*

   A recent evidence based recommendation for the diagnosis, management and prognostication of PH
4. Arena R, Myers J, Guazzi M. The future of aerobic exercise testing in clinical practice: is it the ultimate vital sign? Future Cardiol. 2010;6:325-342
5. Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary exercise testing in patients with pulmonary arterial hypertension: an evidence-based review. J Heart Lung Transplant. 2010;29:159-173
6. Arena R, Guazzi M, Myers J, Grinnen D, Forman DE, Lavie CJ. Cardiopulmonary exercise testing in the assessment of pulmonary hypertension. Expert Rev Respir Med. 2011;5:281-293
7. Arena R, Myers J, Williams MA et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. Circulation. 2007;116:329-343
8. Waxman AB. Exercise physiology and pulmonary arterial hypertension. Prog Cardiovasc Dis. 2012;55:172-9
9. Naeije R, Chesler N. Pulmonary circulation at exercise. Compr Physiol. 2012;2:711–741*

   A detailed review on the response of the pulmonary circulation to exercise
10. Arena R, Cahalin LP, Borghi-Silva A, Myers J. The Effect of Exercise Training on the Pulmonary Arterial System in Patients with Pulmonary Hypertension. Progress Cardiovasc Dis 2015;57:480-8

11. Naeije R, Vanderpool R, Dhakal BP, Saggar R, Saggar R, Vachiery JL, Lewis GD. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. Am J Respir Crit Care Med. 2013 Mar 15;187(6):576-83
12. Herve P, Lau EM, Sitbon O, Savale L, Montani D, Godinas L, Lador F, Jaïs X, Parent F, Günther S, Humbert M, Simonneau G, Chemla D. Criteria for diagnosis of exercise pulmonary hypertension. Eur Respir J. 2015 Sep;46(3):728-37
13. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. Circulation. 2008 Nov 18;118(21):2183-9
14. Dell'Italia LJ. Anatomy and physiology of the right ventricle. Cardiol Clin. 2012;30:167-87
15. Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB; International Right Heart Failure Foundation Scientific Working Group. Right heart failure: toward a common language. J Heart Lung Transplant. 2014;33:123-6
16. Haddad F, Hunt SA, Rosenthal DN, Murphy DJ. Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. Circulation. 2008 Mar 18;117(11):1436-48
17. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation. 2008 Apr 1;117(13):1717-31
18. Naeije R, Brimioulle S, Dewachter L. Biomechanics of the right ventricle in health and disease (2013 Grover Conference series). Pulm Circ. 2014;4:395-406
19. Roberts JD, Forfia PR. Diagnosis and assessment of pulmonary vascular disease by Doppler echocardiography. Pulm Circ. 2011;1:160-81
20. Spruijt OA, de Man FS, Groepenhoff H, Oosterveer F, Westerhof N, Vonk-Noordegraaf A, 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;191(9):1050-7
21. Babu AS, Myers J, Arena R, Maiya AG, Padmakumar R. Exercise testing methods in the evaluation of patients with pulmonary artery hypertension. Expert Rev Cardiovasc Ther 2013;11:729-737
22. Sun XG, Hansn JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104: 429-435**
A seminal paper identifying exercise limitations in pulmonary hypertension
23. Morgan JM, Griffiths M, du Bois RM, Evans TW. Hypoxic pulmonary vasoconstriction in systemic sclerosis and primary pulmonary hypertension. Chest. 1991;99(3):551-6
24. Tolle J, Waxman A, Systrom D. Impaired systemic oxygen extraction at maximum exercise in pulmonary hypertension. Med Sci Sports Exerc. 2008;40:3-8
25. Batt J, Ahmed SS, Correa J, Bain A, Granton J. Skeletal muscle dysfunction in idiopathic pulmonary arterial hypertension. Am J Respir Cell Mol Biol. 2014 Jan;50(1):74-86

26. Breda AP, Pereira de Albuquerque AL, Jardim C, Morinaga LK, Suesada MM, Fernandes CJ, Dias B, Lourenço RB, Salge JM, Souza R. Skeletal muscle abnormalities in pulmonary arterial hypertension. PLoS One. 2014 Dec 2;9(12):e114101
27. Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kubler W, Haass M. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. Circulation 2001;103(17):2153-2158.
28. Kabitz HJ, Schwoerer A, Bremer HC, Sonntag F, Walterspacher S, Walker D, Schaefer V, Ehlken N, Staehler G, Halank M, et al. Impairment of respiratory muscle function in pulmonary hypertension. Clin Sci (Lond) 2008;114(2):165-171
29. de Man FS, van Hees HW, Handoko ML, Niessen HW, Schalij I, Humbert M, Dorfmuller P, Mercier O, Bogaard HJ, Postmus PE, et al. Diaphragm muscle fiber weakness in pulmonary hypertension. Am J Respir Crit Care Med 2011;183(10):1411-1418
30. Fowler RM, Gain KR, Gabbay E. Exercise intolerance in pulmonary arterial hypertension. Pulm Med. 2012;2012:359204. doi: 10.1155/2012/359204
31. Bauer R , Dehnert C, Schoene P, Filusch A, Bärtsch P, Borst MM, Katus HA, Meyer FJ. Skeletal muscle dysfunction in patients with idiopathic pulmonary arterial hypertension. Respir Med. 2007;101:2366-9
32. Meyer FJ, Lossnitzer D, Kristen AV, Schoene AM, Kubler W, Katus HA, Borst MM. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. Eur Respir J 2005: 25: 125-130
33. Ramos RP, Arakaki JS, Barbosa P, Treptow E, Valois FM, Ferreira EV, Nery LE, Neder JA. Heart rate recovery in pulmonary arterial hypertension: relationship with exercise capacity and prognosis. Am Heart J 2012;163:580-8
34. Minai OA, Gudavalli R, Mummadi S, Liu X, McCarthy K, Dweik RA. Heart rate recovery predicts clinical worsening in patients with pulmonary arterial hypertension. Am J Respir Crit Care Med 2012;185: 400–408
35. Wang S, Aurora AB, Johnson BA, Qi X, McAnally J, Hill JA, Richardson JA, Bassel-Duby R, Olson EN. The endothelial-specific microRNA miR-126 governs vascular integrity and angiogenesis. Dev Cell. 2008;15:261-71
36. Potus F, Malenfant S, Graydon C, Mainguy V, Tremblay E, Breuils-Bonnet S, Ribeiro F, Porlier A, Maltais F, Bonnet S, Provencher S. Impaired angiogenesis and peripheral muscle microcirculation loss contribute to exercise intolerance in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2014;190:318-2
37. Bertero T, Lu Y, Annis S, Hale A, Bhat B, Saggar R, Saggar R, Wallace WD, Ross DJ, Vargas SO, Graham BB, Kumar R, Black SM, Fratz S, Fineman JR, West JD, Haley KJ, Waxman AB, Chau BN, Cottrill KA, Chan SY. Systems-level regulation of microRNA networks by miR-130/301 promotes pulmonary hypertension. J Clin Invest. 2014 Aug 1;124:3514-28

38. Kitzman DW, Groban L. Exercise Intolerance. Cardiol Clin 2011;29:461-477
39. Downing J, Balady GJ. The role of exercise training in heart failure. J Am Coll Cardiol. 2011;58:561-9
40. Conraads VM, Van Craenenbroeck EM, De Maeyer C, Van Berendoncks AM, Beckers PJ, Vrints CJ. Unraveling new mechanisms of exercise intolerance in chronic heart failure: role of exercise training. Heart Fail Rev. 2013;18:65-77
41. Guazzi M, Arena R. Pulmonary hypertension with left-sided heart disease. Nat Rev Cardiol 2010;7:648-59
42. Vachiéry JL, Adir Y, Barberà JA, Champion H, Coghlan JG, Cottin V, De Marco T, Galiè N, Ghio S, Gibbs JS, Martinez F, Semigran M, Simonneau G, Wells A, Seeger W. Pulmonary hypertension due to left heart diseases. J Am Coll Cardiol. 2013;62(25 Suppl):D100-8
43. Meyer P, Filippatos GS, Ahmed MI, et al. Effects of right ventricular ejection fraction on outcomes in chronic systolic heart failure. Circulation. 2010;121:252–258
44. Guazzi M. Pulmonary hypertension in heart failure preserved ejection fraction: prevalence, pathophysiology, and clinical perspectives. Circ Heart Fail 2014;7:367-77
45. Borlaug BA. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction. Circ J. 2014;78:20-32
46. Magne J, Pibarot P, Sengupta PP, Donal E, Rosenhek R, Lancellotti P. Pulmonary Hypertension in Valvular Disease: A Comprehensive Review on Pathophysiology to Therapy From the HAVEC Group. JACC Cardiovasc Imaging. 2015;8:83-99
47. Nellessen U, Inselmann G, Ludwig J, Jahns R, Capell AJ, Eigel P. Rest and exercise hemodynamics before and after valve replacement--a combined Doppler/catheter study. Clin Cardiol. 2000;23:32-8
48. Guazzi M, Adams V, Conraads V et al. Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. Circulation 2012;126: 2261-2274
49. Ferrazza AM, Martolini D, Valli G, Palange P. Cardiopulmonary exercise testing in the functional and prognostic evaluation of patients with pulmonary diseases. Respiration. 2009;77:3-17
50. Weitzenblum E, Chaouat A, Kessler R. Pulmonary hypertension in chronic obstructive pulmonary disease. Pneumonol Alergol Pol. 2013;81:390-8
51. Man WD, Kemp P, Moxham J, Polkey MI. Exercise and muscle dysfunction in COPD: implications for pulmonary rehabilitation. Clin Sci (Lond). 2009; 117:281-91
52. Maltais F, Decramer M, Casaburi R, Barreiro E, Burelle Y, Debigaré R, Dekhuijzen PN, Franssen F, Gayan-Ramirez G, Gea J, Gosker HR, Gosselink R, Hayot M, Hussain SN, Janssens W, Polkey MI, Roca J, Saey D, Schols AM, Spruit MA, Steiner M, Taivassalo T, Troosters T, Vogiatzis I, Wagner PD; ATS/ERS Ad Hoc Committee on Limb Muscle Dysfunction in COPD. An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2014;189:e15-

53. Oliveira MF, Zelt JT, Jones JH, Hirai DM, O'Donnell DE, Verges S, Neder JA. Does impaired O2 delivery during exercise accentuate central and peripheral fatigue in patients with coexistent COPD-CHF? Front Physiol. 2015 Jan 7;5:514. doi: 10.3389/fphys.2014.00514
54. Mathur S, Brooks D, Carvalho CR. Structural alterations of skeletal muscle in COPD. Front Physiol. 2014 Mar 19;5:104. doi: 10.3389/fphys.2014.00104
55. Arena R. Exercise Testing and Training in Chronic Lung Disease and Pulmonary Arterial Hypertension. Progress in Cardiovascular Diseases. 2011;53:454-463
56. Boutou AK, Pitsiou GG, Siakka P, Dimitroulas T, Paspala A, Sourla E, Chavouzis N, Garyfallos A, Argyropoulou P, Stanopoulos I. Phenotyping Exercise Limitation in Systemic Sclerosis: The Use of Cardiopulmonary Exercise Testing. Respiration. 2016;91(2):115-23
57. Dumitrescu D, Oudiz RJ, Karpouzas G, Hovanesyan A, Jayasinghe A, Hansen JE, Rosenkranz S, Wasserman K. Developing pulmonary vasculopathy in systemic sclerosis, detected with non-invasive cardiopulmonary exercise testing. PLoS One. 2010;5(12):e14293
58. Boutou AK, Pitsiou GG, Trigonis I, Papakosta D, Kontou PK, Chavouzis N, Nakou C, Argyropoulou P, Wasserman K, Stanopoulos I. Exercise capacity in idiopathic pulmonary fibrosis: the effect of pulmonary hypertension. Respirology. 2011;16(3):451-8
59. Hellebrandová L, Chlumský J, Vostatek P, Novák D, Rýznarová Z, Bunc V. Airflow limitation is accompanied by diaphragm dysfunction. Physiol Res. 2016 Apr 12. [Epub ahead of print]
60. Holland AE. Exercise limitation in interstitial lung disease - mechanisms, significance and therapeutic options. Chron Respir Dis. 2010;7(2):101-11
61. Faisal A, Alghamdi BJ, Ciavaglia CE, Elbehairy AF, Webb KA, Ora J, Neder JA, O'Donnell DE. Common Mechanisms of Dyspnea in Chronic Interstitial and Obstructive Lung Disorders. Am J Respir Crit Care Med. 2016 Feb 1;193(3):299-309
62. Menzel T, Wagner S, Kramm T, Mohr-Kahaly S, Mayer E, Braeuninger S, Meyer J. Pathophysiology of impaired right and left ventricular function in chronic embolic pulmonary hypertension: changes after pulmonary thromboendarterectomy. Chest. 2000;118:897-903
63. Lang IM, Simonneau G, Pepke-Zaba JW, Mayer E, Ambrož D, Blanco I, Torbicki A, Mellemkjaer S, Yaici A, Delcroix M. Factors associated with diagnosis and operability of chronic thromboembolic pulmonary hypertension. A case-control study. Thromb Haemost. 2013 Jul;110(1):83-91
64. Iwase T, Nagaya N, Ando M, Satoh T, Sakamaki F, Kyotani S, Takaki H, Goto Y, Ohkita Y, Uematsu M, Nakanishi N, Miyatake K. Acute and chronic effects of surgical thromboendarterectomy on exercise capacity and ventilatory efficiency in

patients with chronic thromboembolic pulmonary hypertension. Heart. 2001;86:188–192

65. Bonderman D, Martischnig AM, Vonbank K, Nikfardjam M, Meyer B, Heinz G, Klepetko W, Naeije R, Lang IM. Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. Chest. 2011 Jan;139(1):122-127
66. Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. J Am Heart Assoc. 2015 Mar 23;4(3):e001602
67. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J. 2012;39:112-8.
68. Potoka KP, Gladwin MT. Vasculopathy and Pulmonary Hypertension in Sickle Cell Disease. Am J Physiol Lung Cell Mol Physiol. 2014 Nov 14:ajplung.00252.2014. doi:10.1152/ajplung.00252.2014. [Epub ahead of print]
69. Machado RF, Farber HW. Pulmonary hypertension associated with chronic hemolytic anemia and other blood disorders. Clin Chest Med. 2013;34:739-52
70. Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Respir Crit Care Med. 2007; 175:1272–9
71. Balady GJ, Arena R, Sietsema K et al. Clinician's Guide to Cardiopulmonary Exercise Testing in Adults. A Scientific Statement From the American Heart Association. Circulation. 2010;122:191-225
72. 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; American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128:873-934
73. Skalski J, Allison TG, Miller TD. The safety of cardiopulmonary exercise testing in a population with high-risk cardiovascular diseases. Circulation. 2012;126:2465-72
74. Abumehdi MR, Wardle AJ, Nazzal R, Charalampopoulos A, Schulze-Neick I, Derrick G, Moledina S, Giardini A. Feasibility and safety of cardiopulmonary exercise testing in children with pulmonary hypertension. Cardiol Young. 2015 Sep 16:1-7
75. Pinkstaff SO, Burger CD, Daugherty J, Bond S, Arena R. Cardiopulmonary exercise testing in patients with pulmonary hypertension: Clinical recommendations based on a review of the evidence. Exp Rev Resp Med 2016 (Epub ahead of print)*

76. Held M, Grün M, Holl R, Hübner G, Kaiser R, Karl S, Kolb M, Schäfers HJ, Wilkens H, Jany B. Cardiopulmonary exercise testing to detect chronic thromboembolic pulmonary hypertension in patients with normal echocardiography. Respiration. 2014;87:379-87
77. ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med 2002;166:111–117
78. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, McCormack MC, Carlin BW, Sciurba FC, Pitta F, Wanger J, MacIntyre N, Kaminsky DA, Culver BH, Revill SM, Hernandes NA, Andrianopoulos V, Camillo CA, Mitchell KE, Lee AL, Hill CJ, Singh SJ. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44:1428-46
79. Mathai SC, Puhan MA, Lam D, Wise RA. The minimal important difference in the 6-minute walk test for patients with pulmonary arterial hypertension. Am J Respir Crit Care Med. 2012;186:428-33
80. Bellet RN, Adams L, Morris NR. The 6-minute walk test in outpatient cardiac rehabilitation: Validity, reliability and responsiveness – a systematic review. Physiotherapy 2012;98:277-286.
81. Du H, Newton PJ, Salamonson Y, Carrieri-Kohlman VL, Davidson PM. A review of the six-minute walk test: Its implications as a self-administered assessment tool. Eur J Cardiovasc Nurs 2009;8:2-8
82. Deboeck G, Niset G, Vachiery JL, Moraine JJ, Naeije R. Physiological response to the six-minute walk test in pulmonary arterial hypertension. Eur Respir J 2005; 26: 667–672
83. Sherrill DL. Reference Equations for the Six-Minute Walk in Healthy Adults. Am J Respir Crit Care Med 1998; 158:1384–1387
84. Srikanth AM, D'souza GA, Devaraj V, Lucas A. Reference equations for the six-minute walk distance in the Indian population.[abstract] Chest 2006; 130 (suppl): 119S
85. Poh H, Eastewood PR, Cecins NM, Ho KT, Jenkins SC. Six-minute walk distance in healthy Singaporean adults cannot be predicted using reference equations derived from Caucasian populations. Respirology 2006;11:211–216
86. Neal JE, Lee AS, Burger CD. Submaximal exercise testing may be superior to the 6-min walk test in assessing pulmonary arterial hypertension disease severity. Clin Respir J. 2014;8:404-9
87. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, Voigt JU, Zamorano JL; European Association of Echocardiography. Stress echocardiography expert consensus statement: European Association of

Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008;9:415-37

88. Douglas PS, Khandheria B, Stainback RF, Weissman NJ, Peterson ED, Hendel RC, Stainback RF, Blaivas M, Des Prez RD, Gillam LD, Golash T, Hiratzka LF, Kussmaul WG, Labovitz AJ, Lindenfeld J, Masoudi FA, Mayo PH, Porembka D, Spertus JA, Wann LS, Wiegers SE, Brindis RG, Douglas PS, Hendel RC, Patel MR, Peterson ED, Wolk MJ, Allen JM; American College of Cardiology Foundation; American Society of Echocardiography; American College of Emergency Physicians; American Heart Association; American Society of Nuclear Cardiology; Society for Cardiovascular Angiography and Interventions; Society of Cardiovascular Computed Tomography; Society for Cardiovascular Magnetic Resonance.
ACCF/ASE/ACEP/AHA/ASNC/SCAI/SCCT/SCMR 2008 appropriateness criteria for stress echocardiography: a report of the American College of Cardiology Foundation Appropriateness Criteria Task Force, American Society of Echocardiography, American College of Emergency Physicians, American Heart Association, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance endorsed by the Heart Rhythm Society and the Society of Critical Care Medicine. J Am Coll Cardiol. 2008;51:1127-47
89. Grünig E, Tiede H, Enyimayew EO, Ehlken N, Seyfarth HJ, Bossone E, D'Andrea A, Naeije R, Olschewski H, Ulrich S, Nagel C, Halank M, Fischer C. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. Circulation. 2013;128:2005-15
90. Argiento P, Chesler N, Mule M, D'Alto M, Bossone E, Unger P, Naeije R. Exercise stress echocardiography for the study of the pulmonary circulation. Eur Respir J 2010; 35: 1273–1278
91. Maron BA, Cockrill BA, Waxman AB, Systrom DM. The Invasive Cardiopulmonary Exercise Test. Circulation. 2013;127:1157-1164
92. Berry NC, Manyoo A, Oldham WM, Stephens TE, Goldstein RH, Waxman AB, Tracy JA, Leary PJ, Leopold JA, Kinlay S, Opotowsky AR, Systrom DM, Maron BA. Protocol for exercise hemodynamic assessment: performing an invasive cardiopulmonary exercise test in clinical practice. Pulm Circ. 2015 Dec;5(4):610-8
93. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624
94. Yuan P, Yuan XT, Sun XY, Pudasaini B, Liu JM, Hu QH. Exercise training for pulmonary hypertension: A systematic review and meta-analysis. Int J Cardiol 2014; 178C:142-146

95. Buys R, Avila A, Cornelissen VA. Exercise training improves physical fitness in patients with pulmonary arterial hypertension: a systematic review and meta-analysis of controlled trials. BMC Pulm Med. 2015;15:40.
96. Pandey A, Garg S, Khunger M, Garg S, Kumbhani DJ, Chin KM, Berry JD. Efficacy and Safety of Exercise Training in Chronic Pulmonary Hypertension: Systematic Review and Meta-Analysis. Circ Heart Fail. 2015 Nov;8(6):1032-43
97. Babu AS, Padmakumar R, Maiya AG, Mohapatra AK, Kamath RL. Effects of Exercise Training on Exercise Capacity in Pulmonary Arterial Hypertension: A Systematic Review of Clinical Trials. Heart Lung Circ. 2015 Nov 18 [Epub ahead of print]
98. Ehlken N, Lichtblau M, Klose H, Weidenhammer J, Fischer C, Nechwatal R, Uiker S, Halank M, Olsson K, Seeger W, Gall H, Rosenkranz S, Wilkens H, Mertens D, Seyfarth HJ, Opitz C, Ulrich S, Egenlauf B, Grünig E. Exercise training improves peak oxygen consumption and haemodynamics in patients with severe pulmonary arterial hypertension and inoperable chronic thrombo-embolic pulmonary hypertension: a prospective, randomized, controlled trial. Eur Heart J. 2016 Jan 1;37(1):35-44
99. Ehlken N, Verduyn C, Tiede H, Staehler G, Karger G, Nechwatal R, Opitz CF, Klose H, Wilkens H, Rosenkranz S, Halank M, Grünig E. Economic evaluation of exercise training in patients with pulmonary hypertension. Lung. 2014;192:359-66
100. Arena R, Myers J, Forman DE, Lavie CJ Guazzi M. Should high-intensity-aerobic interval training become the clinical standard in heart failure? Heart Fail Rev 2013;18:95-105

Box 1: Definition of various exercise physiological terms described in the paper

Term	**Description**
peakVO2	Maximal oxygen consumed during exercise
$P_{ET}CO2$	Partial pressure or maximal concentration of CO_2 at the end of an exhaled breath
O2 pulse	Oxygen uptake per heart beat
VE/VCO_2	Ventilatory equivalent ratio for CO_2
AT	Level of exercise intensity at which there is a steep build up in lactic acid
VD/Vt	This is the ratio of the dead space to the tidal volume

Figure 1: Summary of various mechanisms resulting in exercise intolerance in pulmonary hypertension

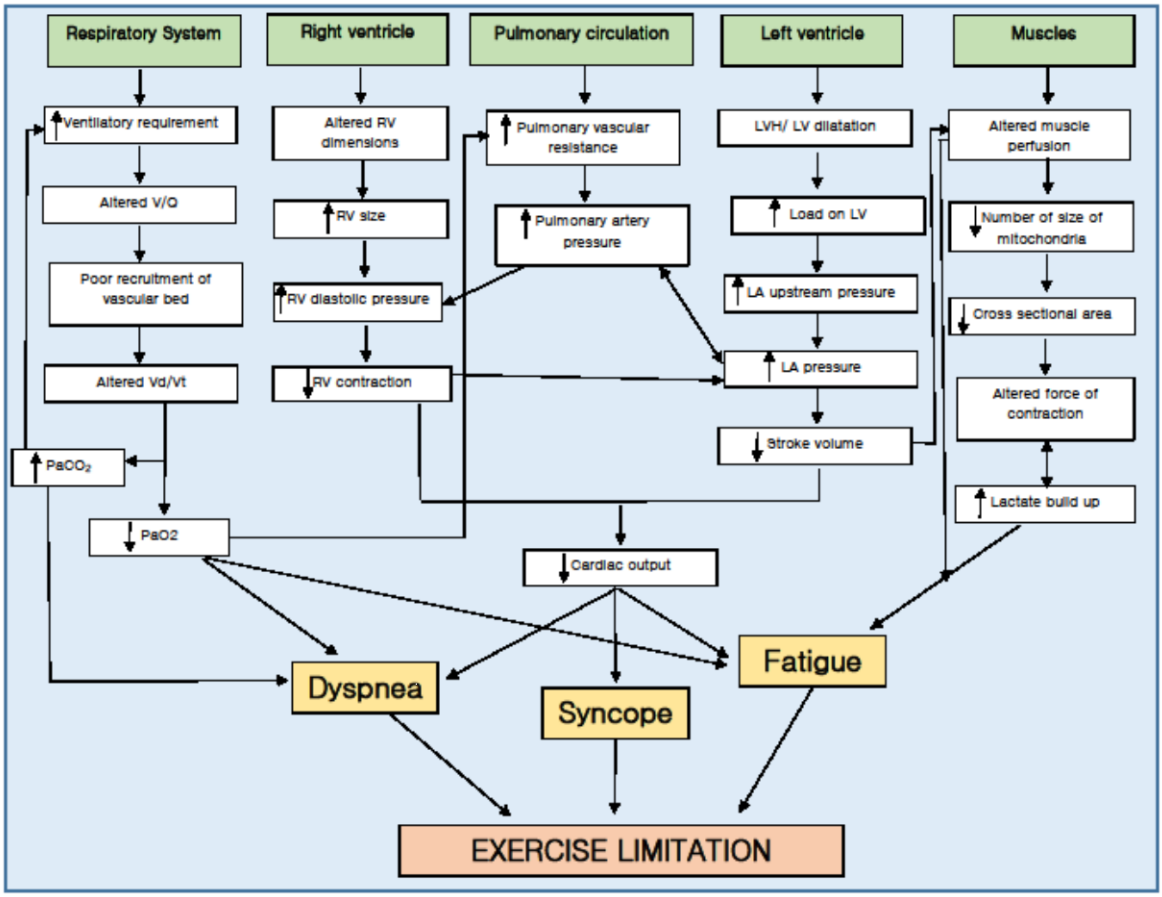

Table 1: Comparison of physiological parameters at peak exercise from ICPX for a normal individual, mild resting PH and exercise induced HF with preserved ejection fraction (HFpEF)

Parameters	Normal individual	Mild resting PH	HFpEF
Work load (Watts)	138	56	113
HR (beats per min)	181	115	123
BP (mmHg)	143/82	163/85	178/91
VO2 (ml/Kg)	2113	814	1877
Qt	15.7	6.8	15.5
SvO2	29	36.4	41.6
SV	87	59	126.1
RAP	10	9	18
PA	38/24	68/18	57/8
mPA	28	40	33
PCWP	16	17	26
PVR	61	271	36

Abbreviations: HR – heart rate; BP – blood pressure; VO2 – oxygen consumption; Qt - ; SvO2 - ; SV – Stroke volume; RAP – right atrial pressure; PA – pulmonary artery; mPA - ; PCWP – pulmonary capillary wedge pressure; PVR – pulmonary vascular resistance.

Table 2: Contribution from various systems to exercise intolerance in PH

PAH group	Pulmonary vascular system	Right ventricle	Left ventricle	Respiratory system	Peripheral muscles	Respiratory muscles	References
I	+++	++	+	+++	+++	++	19,21-24
II	++	++	+++	+	+++	++	31-37
III	++	+++	+	+++	++	+++	10, 42-47
IV	+++	+++	+	+++	++	++	50-52
V*	+	+	+	+	+	+	53-55

+++ - Strong contribution, ++ - moderate contribution, + - weak contribution

*Unclear for group V as there is limited evidence available

Table 3: Studies mentioning prognosis of PAH from CPET

CPET outcome	Findings & interpretation
Peak VO2 < 10.4 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	Survival rate at 1 yr 50% (95% CI = 40-67)
Ve/VCO2 slope >48 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$ Peak VO2 <13.2 ΔO2 pulse <3.3ml/beat	Cummulative survival at 4 yrs 90% (95% CI= 81-98) 71% (95% CI = 56-85) 60% (95% CI = 42-78)
Peak VO2 (%pred) < 34.09 PVR > 1646 dyn·s·cm^{-5} ΔHR < 27 min^{-1}	Survival at 1 and 4 years 70% and 34% 66% and 43% 74% and 33%
Ve/VCO2 at slope AT > 54	Cummulative survival at 4 yrs 69.4%
Ve/VCO2 at slope AT > 55 Ve/VCO2 slope >60	7 fold increase in mortality at 24 months 5 fold increase mortality at 24 months

Reproduced with permission from Babu AS et al (Expert Rev Cardiovasc Ther) – Permission document is uploaded as supporting document

Table 4: Specific exercise recommendations for various PH groups

WHO group	Primary exercise limiting factor (postulated from current evidence)	Proposed exercise training strategy	
Group 1	Abnormal V/Q Peripheral muscles dysfunction	Inspiratory muscle training Strength training	Aerobic training
Group 2	Abnormal perfusion Ventilatory abnormalities	Aerobic training, strength training* Inspiratory muscle training	
Group 3	Ventilatory abnormalities Peripheral muscle dysfunction	Inspiratory muscle training + dyspnea relieving strategies Strength training	
Group 4	Ventilatory abnormalities	Inspiratory muscle training	
Group 5†	Not clear	Not clear	Not clear

*Strength training maybe performed, but with caution

† Insufficient evidence for exercise limiting factors and recommendations.