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

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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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 (L A) 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

\[
PVR = \frac{mPAP - mLAP}{Qp} \quad \text{(Equation 1)}
\]

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:

\[
VO_2 = Qp \times (C_{ao2} - C_{vo2}) \quad \text{(Equation 2)}
\]

where VO\(_2\) is oxygen uptake, Qp is cardiac output and \(C_{ao2}-C_{vo2}\) 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 mPA PA 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. 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. 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). 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.

2.2 Right and Left ventricle

The right ventricle (RV) is a thin walled, crescent shaped chamber that is sensitive to afterload. RV function is regulated through the Frank-Starling mechanism and the autonomic nervous system. Therefore, the RV adapts better to volume overload than pressure overload. 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. 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. 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 LV distensability by the increase in constrain through the pericardium. 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. 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). 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. 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). 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$_{ET}$CO$_2$)] 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$_{ET}$CO$_2$ at the AT. Both VE/VCO$_2$ and P$_{ET}$CO$_2$ 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{22,29} 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.\textsuperscript{22} In addition, contributions from central haemodynamic changes (i.e., reduced RV contractility and SV) further limit exercise performance in these patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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). 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. This parameter was shown to be a strong predictor of clinical worsening in iPAH.

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. 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. 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. 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 coexistence 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.\textsuperscript{38}

A part 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.\textsuperscript{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.\textsuperscript{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\textsubscript{2} slope, peak VO\textsubscript{2}, exercise oscillatory ventilation and the PE\textsubscript{CO\textsubscript{2}}] in a color-coded algorithm.\textsuperscript{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. 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. 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 (VCO₂) 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. In addition to these factors, the role of mitochondrial dysfunction and alterations in arterio-venous oxygen difference, both of which negatively impact peripheral O₂ uptake, further contribute to exercise limitations. The disease process causes significant exercise limitation due to reductions in forced expiratory volume in one second (FEV₁) and tidal volume, in addition to an increase in end expiratory lung volume during exercise resulting in dynamic hyperinflation.

In patients with ILD, ventilatory abnormalities in P₄ETCO₂ and VE / VCO₂ ratios are suggestive of PH. 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 P₄ETCO₂ at rest and during exercise; 2) An increase in the VE/ VCO₂ ratio or slope; and 3) an increase in the Vd/Vt ratio. 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.
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.\textsuperscript{56,57} In addition, $VE/VCO_2@AT$ is another parameter which is very closely related to the presence of PH, especially in patients with ILD.\textsuperscript{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).\textsuperscript{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.\textsuperscript{59} In those with restrictive lung diseases, along with the diaphragmatic dysfunctions, hypoxemic dysfunctions are a major concern in these patients.\textsuperscript{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).\textsuperscript{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. 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.

It has been reported that following endarterectomy, patients improve their exercise performance and quality of life. However, this improvement in peakVO2 did not demonstrate statistical significance in correlation with the PVR (r = −0.41, p = 0.05) and statistically significant correlation observed between the Ve/VCO2 slope and PVR (r = 0.54, p < 0.05). Despite persistence in many patients. 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. 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. 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. In addition, abnormal pulmonary function is common, characterized by a restrictive pattern and abnormal diffusion capacity. 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$_2$. 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\textsubscript{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 e1.10 generally indicating a maximal test.\textsuperscript{71,72} CPX in high risk groups such as PAH has shown to be safe in both adults and children,\textsuperscript{22,73,74} and has been recommended for the screening and prognostication of patients with PH.\textsuperscript{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).\textsuperscript{75}

Ventilatory inefficiency, commonly quantified by the VE/VCO\textsubscript{2} slope or ratio and P\textsubscript{ET}CO\textsubscript{2}, are only obtainable through ventilatory expired gas analysis and these responses have particular value in patients with PAH.\textsuperscript{18,21} The likelihood of PAH during CPX while evaluating persons with dyspnea was demonstrated using key CPX variables such as P\textsubscript{ET}CO\textsubscript{2} and the VE/VCO\textsubscript{2} ratio at the ventilatory threshold (VT).\textsuperscript{50} Patients with P\textsubscript{ET}CO\textsubscript{2} values of > 36 mmHg and VE/VCO\textsubscript{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.\textsuperscript{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.\textsuperscript{76} This scoring system utilizes the VE/VCO\textsubscript{2} slope, the alveolar-arterial oxygen gradient [P(A-a)O\textsubscript{2}], the arterial to end-tidal CO\textsubscript{2} gradient [P(c-ET)CO\textsubscript{2}] and P\textsubscript{ET}CO\textsubscript{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. Recently, an evidence-based review on the validity and reliability of the 6MWT was published by the European Respiratory Society and ATS. 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.

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 $\text{VO}_2$ (ranging between 0.40 and 0.80) including studies assessing patients with PAH.\textsuperscript{80-82} Studies have also developed equations using the 6MWT to predict peak $\text{VO}_2$ in both HF and COPD cohorts, and the estimated values for peak $\text{VO}_2$ have been demonstrated to be reasonable approximations of maximal exercise capacity.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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. A part 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{88}

With regard to PAH, exercise echocardiography has been useful in identifying abnormal pulmonary vascular responses during exercise among those at risk for PAH.\textsuperscript{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:

\[ \text{PASP} = 4(\text{TR velocity})^2 + \text{RAP} \]

An inadequate PASP rise (<30mmHg), during exercise has been demonstrated to predict poor prognosis and poor performance on the 6MWT.\textsuperscript{89} A recent study found TAPSE and the tricuspid annular systolic velocity during bicycle ergometry reflected the RV response to exercise.\textsuperscript{90} Recently, poor linearity in the relationship between oxygen consumption to work rate (\(\text{VO}_2/\text{WR}\)) 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.\textsuperscript{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 \(\text{VO}_2\) and an impaired ventilatory efficiency. This flattening suggests an abnormal pulmonary vascular response to exercise among a group 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. 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

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.

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). 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 HFrEF 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. 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. 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. 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.\textsuperscript{10,94-97} These similar findings were also observed in a recent clinical trial among patients with CTEPH.\textsuperscript{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.\textsuperscript{99}

Moderate intensity exercise (e.g., 50-60% of VO\textsubscript{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.\textsuperscript{32} High intensity interval training has been used in patients with HF, with studies reporting both clinical and physiological benefits following this intervention.\textsuperscript{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 RV's 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
exercising 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. The potential reversibility has been observed in various clinical trials on exercise training in PH. 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.

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 evaluation 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.
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A recent evidence based recommendation for the diagnosis, management and prognostication of PH


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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


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


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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


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

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>peakVO₂</td>
<td>Maximal oxygen consumed during exercise</td>
</tr>
<tr>
<td>$P_{ET}CO₂$</td>
<td>Partial pressure or maximal concentration of CO₂ at the end of an exhaled breath</td>
</tr>
<tr>
<td>O₂ pulse</td>
<td>Oxygen uptake per heart beat</td>
</tr>
<tr>
<td>VE/VCO₂</td>
<td>Ventilatory equivalent ratio for CO₂</td>
</tr>
<tr>
<td>AT</td>
<td>Level of exercise intensity at which there is a steep build up in lactic acid</td>
</tr>
<tr>
<td>VD/Vt</td>
<td>This is the ratio of the dead space to the tidal volume</td>
</tr>
</tbody>
</table>
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)

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

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

<table>
<thead>
<tr>
<th>PAH group</th>
<th>Pulmonary vascular system</th>
<th>Right ventricle</th>
<th>Left ventricle</th>
<th>Respiratory system</th>
<th>Peripheral muscles</th>
<th>Respiratory muscles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>19,21-24</td>
</tr>
<tr>
<td>II</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>31-37</td>
</tr>
<tr>
<td>III</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>10,42-47</td>
</tr>
<tr>
<td>IV</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>50-52</td>
</tr>
<tr>
<td>V*</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>53-55</td>
</tr>
</tbody>
</table>

+++ - 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

<table>
<thead>
<tr>
<th>CPET outcome</th>
<th>Findings &amp; interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO2 &lt; 10.4 mL O₂ · kg⁻¹ · min⁻¹</td>
<td>Survival rate at 1 yr</td>
</tr>
<tr>
<td></td>
<td>50% (95% CI = 40-67)</td>
</tr>
<tr>
<td>Ve/VCO₂ slope &gt;48 mL O₂ · kg⁻¹ · min⁻¹</td>
<td>Cumulative survival at 4 yrs</td>
</tr>
<tr>
<td>Peak VO2 &lt;13.2</td>
<td></td>
</tr>
<tr>
<td>ΔO2 pulse &lt;3.3ml/beat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>90% (95% CI = 81-98)</td>
</tr>
<tr>
<td></td>
<td>71% (95% CI = 56-85)</td>
</tr>
<tr>
<td></td>
<td>60% (95% CI = 42-78)</td>
</tr>
<tr>
<td>Peak VO2 (%pred) &lt; 34.09</td>
<td>Survival at 1 and 4 years</td>
</tr>
<tr>
<td>PVR &gt; 1646 dyn·s·cm⁻⁵</td>
<td></td>
</tr>
<tr>
<td>ΔHR &lt; 27 min⁻¹</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70% and 34%</td>
</tr>
<tr>
<td></td>
<td>66% and 43%</td>
</tr>
<tr>
<td></td>
<td>74% and 33%</td>
</tr>
<tr>
<td>Ve/VCO₂ at slope AT &gt; 54</td>
<td>Cumulative survival at 4 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.4%</td>
</tr>
<tr>
<td>Ve/VCO₂ at slope AT &gt; 55</td>
<td>7 fold increase in mortality at 24 months</td>
</tr>
<tr>
<td></td>
<td>5 fold increase mortality at 24 months</td>
</tr>
</tbody>
</table>

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### Table 4: Specific exercise recommendations for various PH groups

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

*Strength training maybe performed, but with caution

† Insufficient evidence for exercise limiting factors and recommendations.