Pulmonary Vascular Hemodynamic Response to Exercise in Cardiopulmonary Diseases

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Pulmonary hypertension (PH), regardless of the pathobiology and site of functional changes, is characterized by an asymptomatic or a latent phase followed by a gradual reduction in exercise capacity related to decreasing right ventricular (RV) contractile reserve. In addition to right heart and pulmonary vascular function, other factors including ventilation/perfusion mismatch, hypoxemia, peripheral oxygen transportation/utilization, and impaired skeletal muscle function, may significantly influence the functional status of patients with PH.

Guidelines provide a clinical classification system that categorizes PH into 5 groups with specific pathogenesis, pathologies, and clinical characteristics. The natural history of the disease is determined by the rapidity of increase in resting mean pulmonary artery pressure (mPAP) and the ability of the RV to compensate and hypertrophy, which differs depending on the pathobiology and related diseases. The definition of PH and PH groups is based on clinical assessment and invasive hemodynamics. Precapillary PH (groups 1 and 3–5) is characterized as a resting mPAP of ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) or left ventricular (LV) end-diastolic pressure ≤15 mm Hg. Postcapillary PH (group 2) is associated with an elevated pulmonary venous pressure (>15 mm Hg) related to left heart disease, which may involve abnormalities of the LV, mitral valve, or aortic valve. Although the group definitions for PH are helpful, in clinical practice, it is not uncommon for patients to have >1 disease associated with PH and to have both precapillary and postcapillary components, so called multifactorial PH (eg, aortic stenosis, systemic sclerosis, chronic thromboembolic disease) or out-of-proportion PH for a given condition (eg, chronic lung disease, chronic heart failure).

The concept that symptoms associated with cardiopulmonary diseases would be associated with an abnormal increase in mPAP with exercise was demonstrated >60 years ago. Since then, there has been considerable investigation by clinical scientists. The PH guidelines published in 2009 removed out-of-proportion PH for a given condition (eg, chronic lung disease, chronic heart failure).

Here, we present the normal pulmonary vascular and physiological responses of the right side of the heart to exercise, the responses in each of the major causes of PH, and the potential clinical and investigative utility of assessing hemodynamics by exercise testing.

Physiology of the Pulmonary Circulation at Rest and During Exercise

Exercise stresses the pulmonary circulation through an increase in cardiac output (CO) and mean left atrial pressure (LAP), each of which results in an increase in mPAP. The relationships between mPAP, CO, and LAP are defined by the pulmonary vascular resistance (PVR) equation:

\[ PVR = \frac{mPAP - LAP}{CO}. \] (1)

The PVR equation rewritten as \( mPAP = PVR \times CO + LAP \) shows how much mPAP increases with CO or LAP at any given PVR. More than 50 years ago, Paul Wood reported that mPAP does not exceed 20 mm Hg at rest as long as PVR, CO, and LAP remain within normal limits. As discussed earlier, PH has been defined by an mPAP at rest ≥25 mm Hg. An mPAP of 21 to 24 mm Hg corresponds to so-called “borderline PH” of still undetermined clinical relevance. PH can be caused by abnormally high PVR, CO, or LAP.

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The inherent assumptions of the PVR equation are that (mPAP–LAP)/CO relationships are linear and cross the line of origin. If these assumptions are correct, PVR should be independent of absolute levels of pressure and flow and of measurements at exercise predicted from resting values. However, it has been shown that exercise is normally associated with a decrease in PVR. The exercise-induced decrease in PVR is attributable to pulmonary vascular recruitment in the setting of increased PAP and flow, as well as the distensibility of the normal pulmonary resistance vessels. This decrease is greater when exercise is performed in the upright position because of higher resting PVR resulting from incomplete recruitment of pulmonary resistance vessels in the upper portions of the lungs at rest. The supine position and mild to moderate exercise allow complete pulmonary vascular recruitment. Most of the exercise-induced decrease in PVR is explained by distension of the pulmonary resistance vessels.

Because resistance vessels are distensible, multipoint mPAP/CO relationships normally present with a slight curvilinearity (Figure 1). Adjustment of these pressure-flow curves with a mathematical model of the pulmonary circulation allows for a recalculation of a distensibility coefficient, \( \alpha \), which can be introduced into a refined PVR equation for an improved estimation of mPAP at various COs or LAPs:

\[
mPAP = \frac{1}{\alpha} \left( 1 + \alpha LA P \right)^{\frac{1}{5}} + 5 \alpha R_0 Q \right)^{\frac{1}{5}} - 1
\]

where \( R_0 \) is PVR and \( Q \) is pulmonary blood flow. The distensibility coefficient \( \alpha \) defines how much resistance vessel diameters increase as a percent of baseline per mmHg distending pressure. The normal value of \( \alpha \) is 2% per mmHg. This value has been established in pulmonary vessels mounted in vitro and is remarkably constant from one species to another. The coefficient \( \alpha \) is higher in pre-menopausal women as compared to men and decreases with age. A seemingly-modest 2% distensibility of pulmonary resistive vessels is actually a major cause of the limitation of increase in mPAP and decrease in PVR normally observed with exercise (Figure 2). The sensitivity of \( \alpha \) to early pulmonary vascular disease is currently under investigation.

In patients with cardiac or pulmonary diseases, PVR has been reported to decrease during exercise in some studies, but other studies have reported unchanged or even increased PVR during exercise, depending on body position and workload. In general, an exercise-induced increase in PVR may be observed in heart failure and pulmonary vascular disease when resting measurements are performed in the supine position and when patients perform maximum tolerated exercise. In most situations, the number of recovered mPAP/CO coordinates remains limited when workload is moderate. In these circumstances, multipoint mPAP/CO plots are best described by a linear approximation. Such a dynamic PVR still offers a more robust definition of the functional state of the pulmonary circulation than a single-point PVR.

Invasive as well as non-invasive studies in healthy volunteers show that the slope of “linearized” mPAP/CO relationships ranges from 0.5 to 3.0 mmHg/L/min (Table 1). LAP increases during exercise with upstream transmission to mPAP. The increment in LAP during exercise also reduces pulmonary compliance and thereby leads to an increase in transpulmonary pressure gradient (mPAP minus LAP = TG; Figure 3). However, LAP exceeds the upper limit of resting normal in healthy young adult subjects only at very high cardiac outputs, in the range of 20 L/min and greater. The pulmonary capillary wedge pressure (PCWP) to estimate LAP can increase to as high as 25mmHg in exercising athletes. In fact, as reviewed by West, at very high levels of exercise elite athletes may develop pulmonary edema and changes in the integrity and function of the blood-gas barrier that results in ‘exercise induced pulmonary hemorrhage’, a phenomenon common to race horses. In older subjects and particularly in heart failure patients, steep increases in LAP or PCWP are apparent during early exercise and contribute to mPAP/CO > 3.0mmHg/L/min. A disproportionate increase in LAP or PCWP affects mPAP at lower levels of

Figure 1. Limits of normal of mean pulmonary artery pressure (mPAP) as a function of cardiac output (CO) at exercise in healthy young adults, constructed from multipoint noninvasive (n=113) and invasive (n=24) measurements reported in ref 7. All baseline resting measurements were within the limits of normal. No slope of linearized mPAP-CO relationships exceeded 3 mmHg/L/min. Slopes of mPAP-CO and derived distensibility calculations were identical in noninvasive and invasive studies. Stippled lines indicate upper limits of mPAP at specified cardiac outputs.

Figure 2. Modeled mean pulmonary arterial pressure-cardiac output (mPAP-Q) relationships during dynamic exercise with progressively increased distensibility coefficients (\( \alpha \)). The normal range of \( \alpha \) values is 1-2%. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. Adapted from reference 7, reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society.
exercise in older subjects\textsuperscript{5} and at very low levels of exercise in heart failure patients.\textsuperscript{5,16}

Cardiac and pulmonary diseases may affect mPAP by increased PVR, increased LAP, and sometimes an increased CO. The limited data available point to a prominent effect of increased PVR as a cause of steeper mPAP/CO plots. A disproportionate increase in mPAP, ie, more than predicted from the resting PVR equation, may also be due to pulmonary vasoconstriction related to low mixed venous PO\textsubscript{2}, acidosis and sympathetic nervous system activation.\textsuperscript{5,17} Exercise-induced pulmonary vasoconstriction typically causes extrapolated pressure intercepts of mPAP/CO plots to be negative.\textsuperscript{16}

When a sufficient number of mPAP-CO coordinates are generated, it becomes possible to identify patterns.\textsuperscript{11,12,16} Both linear and “take-off” patterns of mPAP-CO relationships have been observed in patients with left heart failure.\textsuperscript{11,16} A take-off pattern is explained by increased LAP or pulmonary vasoconstriction. A “plateau pattern” may emerge, particularly when CO at still-increasing \(V_o2\) at the highest level of exercise may explain “plateauing” of the mPAP-\(V_o2\) relationship in PAH.\textsuperscript{12}

Recent studies have begun to clarify the clinical correlates of exercise-induced PH.\textsuperscript{11,12} Invasive and noninvasive studies have accumulated, showing that the slope of linearized mPAP-CO relationships should not exceed 3 mm Hg L\textsuperscript{-1} min\textsuperscript{-1} (Figure 1 and the Table\textsuperscript{6,9–12,16,18–32}). This corresponds to the former definition of exercise-induced PH (mPAP >30 mm Hg) provided that CO remains <10 L/min or total pulmonary resistance (mPAP/CO) at maximum exercise is <3 Wood units.

Although further work is needed to improve exercise testing protocols for the diagnosis and follow-up of PH, several guiding principles and limitations deserve mention. Exercise should be dynamic, avoiding the increase in systemic vascular resistance and abrupt changes in intrathoracic pressure that occur with resistive exercise and might present with unpredictable effects on the pulmonary circulation. Even with dynamic exercise, however, increased ventilation causes pulmonary vascular pressures to vary greatly between inspiration and expiration, as reflected by respiratory swings of esophageal pressures. Therefore, measuring pulmonary vascular pressures at end expiration, when esophageal pressures are positive (particularly in obstructive lung disease), may lead to a false diagnosis of exercise-induced PH. It is therefore preferable to average the reading of pulmonary vascular pressures over the entire respiratory cycle. Postexercise measurements are thought to be unreliable because of the rapid return of pulmonary vascular pressures and flows to the baseline resting state. Even though workload or \(V_o2\) and CO are linearly related, they should not be used as surrogates considering that a determinant of pulmonary vascular pressure is flow and the individual variability of workload or \(V_o2\) versus CO relationships is high. Finally, recently developed noninvasive echocardiographic measurements of mPAP-CO relationships have been shown to closely approximate invasively measured mPAP values,\textsuperscript{7,10,25} and may be feasible in highly dedicated centers with very experienced echocardiographers, but they require more validation to demonstrate clinical relevance.

Accepting a cutoff value of a slope of mPAP/CO plots >3 mm Hg L\textsuperscript{-1} min\textsuperscript{-1} or a total PVR >3 Wood units at maximum exercise does not clarify whether the abnormal pressure is attributable to pulmonary vasoconstriction, remodeling, or upstream transmission of a high LAP or PCWP. Thus, a better definition of the limits of normal of LAP at exercise is also needed. In the meantime, it can be safely assumed that the functional state of the pulmonary circulation is best described by >4- to 5-point (mPAP-LAP)/CO plots to calculate a slope (Figure 4).\textsuperscript{31}

**Heart Failure With Reduced LV Ejection Fraction**

Heart failure with reduced LVEF (HFrEF) is commonly associated with the development of pulmonary hypertension (HFrEF-PH). HFrEF-PH purports a poor prognosis, particularly when it is accompanied by RV dysfunction.\textsuperscript{34} Single resting right heart catheter or echocardiography measurements tend to vary with diurnal patterns, autonomic tone, and timing of medication exposures (ie, diuretics), which can confound conclusions about the degree of right ventricular-pulmonary vascular (RV-PV) dysfunction present in HFrEF.\textsuperscript{35} In contrast, exercise permits multiple measurements across varying loading conditions to assess RV contractile reserve and the ability of the pulmonary vasculature to accommodate increased flow.\textsuperscript{36}

A recent study established that exercise in HFrEF elicits a steep increase in mPAP that is attributable to exaggerated increases in both TPG and PCWP.\textsuperscript{11} A steep linear increment in mPAP in response to exercise was independently associated with reduced exercise capacity (peak \(V_o2\)) and reduced survival in patients with HFrEF. Failure to augment mPAP throughout exercise, resulting in a plateau pattern of mPAP versus work over the entire respiratory cycle, is indicative of dynamic RV dysfunction.
and portended a particularly poor prognosis.11 These findings complement previous studies showing that mPAP and PVR responses to exercise are more closely related to outcomes than resting hemodynamic measurements in HFrEF.11 Exercise echocardiography has also been used in the evaluation of HFrEF-PH, although Doppler measures of right- and particularly left-side pressures can be challenging to ascertain during exercise and require further validation. Tumminello et al found that peak exercise pulmonary artery systolic pressure (PASP) in patients with HFrEF was related principally to mitral regurgitation and contractile reserve, whereas Maréchaux et al identified intraventricular dyssynchrony and impaired contractile reserve to be independent predictors of exercise-induced changes in PASP.38 Notably, very low tricuspid annular plane systolic excursion (<14 mm) predicted a more modest maximum increase in PASP during exercise, a finding that mirrors invasive data suggesting that marked impairment in RV performance during exercise leads to a limited capacity to augment PASP and mPAP.11 The aforementioned echocardiography-based studies focused on peak exercise PASP or peak exercise changes in PASP, which are attenuated if CO augmentation is modest during exercise. Therefore, it is preferable to interpret exercise mPAP augmentation patterns relative to increases in blood flow through the pulmonary circulation (mPAP/CO as described previously; see the Table).

Several mechanisms may account for the heightened mPAP/CO observed in HFrEF. Increased left-side pressures during exercise caused by HFrEF are to be expected, but exaggerated increases in TPG are also observed in HFrEF. This may be attributable to maximally recruited pulmonary vasculature at rest on account of elevated resting LV pressures, thus limiting passive recruitment and distension during exercise observed in

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CO indicates cardiac output; COPD, chronic obstructive lung disease; Ex, exercise; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; ΔmPAP/ΔCO, the slope of the pulmonary arterial pressure versus cardiac output during exercise; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; and SSc, systemic scleroderma.
Heart failure with preserved LV ejection fraction (HFpEF) constitutes ≈40% of the heart failure population and is associated with a similar prognosis to HFrEF.41 HFpEF, like HFrEF, is associated with a steep increase in mPAP during exercise (Table). Echocardiography-based mechanistic studies indicate that exercise mPAP in HFpEF, unlike HFrEF, is most closely associated with degree of diastolic dysfunction.42 In both HFrEF and HFpEF, it is important not to overlook comorbid conditions that can contribute to PH such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, valvular heart disease, or chronic thromboembolic PH.

Current guideline-based diagnostic criteria for HFpEF include objective evidence of elevated cardiac filling pressures based on cardiac catheterization, echocardiography, or natriuretic peptide assays.42,43 These criteria lead to potential underdiagnosis of HFpEF in symptomatic patients without hypervolemia. Borlaug et al reported invasive hemodynamic responses to exercise in 55 euvolemic subjects with exertional dyspnea and normal resting hemodynamic measurements.30 A PCWP threshold of ≥25 mm Hg during supine cycle ergometry or weightlifting with the arms was used to diagnose HFpEF. HFpEF subjects experienced significantly greater exercise-induced increases in mPAP (ie, from 19±4 to 42±7 mm Hg; Table) than subjects with noncardiac dyspnea (ie, from 15±4 to 23±5 mm Hg) despite achieving lower peak COs. Exercise PASP is easily amenable to noninvasive measurement. In the same study, exercise PASP identified HFpEF with 96% sensitivity and 95% specificity using a cut point of 45 mm Hg. Exercise PASP outperformed resting PAP, natriuretic peptide levels, and echocardiographic indicators for diagnosing HFpEF.30

Similarly, Kitzman et al reported in 1991 that compensated outpatients with HFpEF had normal resting PCWP but marked increases in exercise PCWP, suggesting that HFpEF may initially manifest with only intermittent elevations in cardiac filling pressures.30 Both studies indicate that exercise hemodynamic measurements are of incremental value for the diagnosis of HFpEF and may provide a window into earlier diagnosis of the condition. However, at present, there is no consensus on the appropriate partition value to define an abnormal exercise PCWP or LV end-diastolic pressure, with suggested cut-off values ranging from 15 to 25 mm Hg. Furthermore, before labeling elevations in exercise hemodynamic measurements as early forms of HFpEF, more information is needed on the natural history of patients with exercise elevations in mPAP and PCWP to determine the rate at which they go on to develop adverse outcomes known to be associated with overt HFpEF.

In addition to assisting with the diagnosis of HFpEF in the setting of normal resting hemodynamic measurements, exercise may be of particular value is assessing the entity of PH out of proportion to LV dysfunction, alternatively called PH–LV dysfunction or mixed PH.45 In mixed PH, the partitioning of relative contributions of PCWP and TPG to exercise mPAP may help to further phenotype patients with dyspnea and to inform targeted interventions directed at either the LV or the pulmonary vasculature. Indeed, a recent trial of phosphodiesterase 5 inhibitor sildenafil has shown to improve exercise PVR and exercise capacity in HFpEF.30,36

A greater knowledge of compensatory responses of the RV–pulmonary vascular unit during exercise in patients with HFpEF may improve our understanding of its functional role in determining exercise capacity while aiding in earlier diagnosis of PH complicating HFpEF and informing targeted therapeutic interventions.36

Heart Failure With Preserved LV Ejection Fraction

Figure 4. Linear mean pulmonary arterial pressure (mPAP)-flow relationships based on averages of serial measurements of mean PAP and cardiac output during incremental exercise. Normal young adults (□), patients with scleroderma with PAP in the lower normal range (♦) and borderline-PH range (▲), and patients with resting PAH (●) demonstrate approximately linear pressure-flow responses during exercise. Despite similar resting mPAP and CO in normals and the two scleroderma subgroups, exercise elicits a steeper increment in mPAP vs. CO in scleroderma borderline-PH group (▲). The mPAP-CO slope of >3.0 (dashed reference line) represents an abnormal pulmonary vascular response to exercise and may be indicative of early pulmonary vasculopathy. Adapted from reference 33. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of the copyright in the translation or adaptation. Reprinted with permission of Advances in Pulmonary Hypertension. Copyright © 2013 Advances in Pulmonary Hypertension.

Heart Failure With Preserved LV Ejection Fraction

Heart failure with preserved LV ejection fraction (HFpEF) constitutes ≈40% of the heart failure population and is associated with a similar prognosis to HFrEF.41 HFpEF, like HFrEF, is associated with a steep increase in mPAP during exercise (Table). Echocardiography-based mechanistic studies indicate that exercise mPAP in HFpEF, unlike HFrEF, is most closely associated with degree of diastolic dysfunction.42 In both HFrEF and HFpEF, it is important not to overlook comorbid conditions that can contribute to PH such as chronic obstructive pulmonary disease (COPD), obstructive sleep apnea, valvular heart disease, or chronic thromboembolic PH.
leading to an increase in PVR, adaptive right heart hypertrophy, and right heart failure.\textsuperscript{1,2} Numerous pathogenic factors and diseases affecting the pulmonary vascular bed have been identified that result in a similar clinical phenotype with impaired exercise capacity, quality of life, and prognosis. The diagnosis of PAH requires confirmation by direct assessment of invasive hemodynamic parameters at rest.\textsuperscript{1,2}

As reviewed by Bossone et al, there have been a limited number of studies that have evaluated invasive hemodynamics during exercise in PAH.\textsuperscript{4} Whereas healthy subjects can achieve a more than 10-fold increase in VO\textsubscript{2} during exercise due to a complex cardiovascular, ventilatory and peripheral response, in PAH patients peak VO\textsubscript{2} is significantly reduced. Patients with PAH are mainly limited by a reduced CO at rest and during exercise and have steep mPAP-CO relationships.\textsuperscript{16} RV dysfunction is the most important factor contributing to functional impairment and mortality.

Despite the lack of adequate standards, there is increasing enthusiasm for performing noninvasive assessment of exercise hemodynamics to screen for PAH and to assess prognosis. As reviewed by Bossone and Naeije,\textsuperscript{2} the clinical phenotype of normal pulmonary arterial pressure at rest and high response during exercise has been evaluated with recumbent exercise echo Doppler studies in subjects at risk for PAH in 10 studies involving 824 subjects (427 with connective tissue disease, 54 with congenital heart disease, and 343 relatives of idiopathic PAH cases).\textsuperscript{3} Although the measurement of PASP during symptom-limited exercise or at given workloads is of interest as a screening tool for PAH, it is not adequate for determining whether the exaggerated exercise-induced increase in PASP in persons with dyspnea or fatigue is attributable to a precapillary (PAH) or postcapillary (pulmonary venous hypertension) source. It may be helpful for selecting high-risk patients who would benefit from direct measurement of invasive hemodynamics at rest and with exercise such as those with a family history of PAH or connective tissue diseases (discussed below).

Grüng et al demonstrated the use of recumbent exercise echo Doppler for identifying asymptomatic family members of idiopathic PAH patients carrying a predisposing mutation in the bone morphogenetic protein receptor II gene in 2 families\textsuperscript{47} and subsequently led a multicenter study in 291 relatives of 109 PAH patients and 191 age-matched control subjects from 6 centers in European countries.\textsuperscript{48} During exercise (mean maximal workload of 148 W in control subjects and 124 W in relatives), 10% of control subjects but 31.6% of the relatives (P<0.0001) exceeded the 90th percentile of mean maximal tricuspid regurgitation velocity of >3.08 m/s (corresponding to PASP of >43 mm Hg) seen in control subjects.

Tolle et al conducted a landmark study demonstrating that the pattern and severity of the invasive hemodynamic response to cycle ergometry exercise (symptom limited with peak heart rate ≥80% of predicted or respiratory exchange ratio of ≥1) in exercise-induced PAH are intermediate between those of the normal subject and those of the patient with resting PAH and provide support for the hypothesis that exercise-induced PAH is a mild yet symptomatic phase of the disease.\textsuperscript{4} Cardiopulmonary exercise testing was used to diagnose the cause of dyspnea or fatigue in 255 patients; of these patients, the concluding diagnosis was PAH in 93 and 16 were considered normal. Of the PAH group, 78 had exercise-induced PAH and 15 had evidence of PAH at rest (mPAP ≥25 mm Hg). The mean (2 SD) mPAP with exercise was 27.4 mm Hg (7.4 mm Hg) in the normal group, 36.6 mm Hg (11.4 mm Hg) in the exercise-induced group, and 48.4 mm Hg (22.2 mm Hg) in those with resting PAH, whereas the PCWP and mRAP did not differ between groups. Consistent with findings in HFrEF, a plateau pattern in PASP versus VO\textsubscript{2} (or CO) in exercise-induced PAH patients was associated with worse functional capacity.\textsuperscript{12} Interestingly, resting mPAP, including those in an “indeterminate” range of 21 to 25 mm Hg, did not reliably predict exercise-induced PAH.

Exercise hemodynamics in idiopathic PAH on PAH-specific treatment correlates much better with improved exercise tolerance than resting hemodynamics. Extending earlier observations by their group, in 2008, Provencher et al evaluated 42 patients with idiopathic PAH at baseline and after PAH-specific treatments for an average of 5 months.\textsuperscript{49} With a 43-m improvement in 6-minute walk distance, on multivariate analysis, improvement was related to changes in cycle exercise (40 W) hemodynamics; specifically, the peak cardiac index was achieved at a lower mPAP, consistent with exercise vasodilation. Whether a change in pressure-flow relationship response (∆mPAP/∆CO; Figures 1 and 2) at a given workload, target heart rate, or percent of aerobic capacity will improve risk stratification and treatment decisions is an important area of future research in PAH.

**Exercise Hemodynamics in Scleroderma**

Patients with scleroderma are considered an at-risk group for developing PH, which when present is the major cause of death.\textsuperscript{1,2} They may have latent or asymptomatic PAH, associated with hypoxemia and lung disease, as well as LV diastolic dysfunction or pulmonary venous hypertension from hypertension or scleroderma cardiomyopathy.\textsuperscript{50,51} Although the definition of PH requires an mPAP ≥ 25 mm Hg, there is evidence that scleroderma patients with a baseline “borderline” resting mPAP of 21 to 24 mm Hg and with exaggerated PAP response to exercise are at higher risk of developing progressive pulmonary vascular disease.\textsuperscript{52,53} This suggests that the hemodynamic response to exercise in scleroderma, as assessed by echo Doppler and heart catheterization, may detect those who are likely to develop rapidly progressive PAH in a preclinical phase that may respond to therapy. The importance of such efforts is supported by several studies. RV diastolic dysfunction has been found in patients with scleroderma and normal resting but abnormal exercise PH (latent PH) scleroderma.\textsuperscript{50} Kovacs and colleagues\textsuperscript{52} reassessed exercise invasive hemodynamics (50 W and maximum exercise) in 10 borderline PAH patients with scleroderma after a 1-year observation period; a progression was noted in pertinent hemodynamic variables (mPA and PVR). Furthermore, in the UK PH registry, one fifth of scleroderma patients with exercise PH developed resting PAH after ≈2.3 years.\textsuperscript{53}

The frequency, spectrum, and significance of a hypertensive PAP response to exercise in scleroderma are currently uncertain. The PAP response may reflect a normal variant (eg, related to age) without clinical significance or a manifestation of abnormal pulmonary arterial vasodilator reserve and may
be composed of precapillary or postcapillary pathological rises in pressure. Saggar et al assessed the invasive hemodynamic response to recumbent submaximal cycle exercise in 57 patients with dyspnea and clinical scleroderma who had normal resting hemodynamics but decreased DICO or a FVC:DICO percent predicted ratio >1.4. Those with an LV ejection fraction <50% or more than mild LV diastolic dysfunction were excluded. They found 4 distinct groups: normal in 26%, exercise pulmonary venous hypertension in 21% (mPA >30 mm Hg, PCWP >18 mm Hg, and TPG <15 mm Hg), exercise out-of-proportion PH in 16% (mPA >30 mm Hg, PCWP >18 mm Hg, and TPG ≥15 mm Hg), and exercise PAH in 37% (mPA >30 mm Hg, PCWP <18 mm Hg, and TPG >15 mm Hg). A baseline mPAP <14 mm Hg was not associated with exercise PH or exercise out-of-proportion PH, whereas a resting mPAP ≥20 mm Hg has a 90% positive predictive value for exercise PH, exercise out-of-proportion PH, or pulmonary venous hypertension, and a concurrent PVR ≥2 Wood units had a positive predictive value of 100%. For those with an mPAP of 14 to 20 mm Hg, a low normal PVR had a negative predictive value of 100%, and a PVR ≥2 Wood units had a positive predictive value of 89% for predicting exercise PH and exercise out-of-proportion PH. In a similar study of 54 patients with scleroderma at risk for PH, of normal PVR had a negative predictive value of 100%, and a PVR ≥2 Wood units had a positive predictive value of 89% for predicting exercise PH and exercise out-of-proportion PH. In a similar study of 54 patients with scleroderma at risk for PH, of the 17 patients with an RV systolic pressure <35 mm Hg at rest and at least a 20-mm Hg increase in RV systolic pressure during stress echo Doppler, during the heart catheterization with exercise conducted by arm exercise with weights, 1 patient had no PH, 3 patients had evidence of LV diastolic dysfunction, and 13 patients had exercise-induced PAH. Finally, a recent uncontrolled, open-label study suggested that chronic oral administration of ambrisentan may be associated with significant improvement in exercise cardiopulmonary hemodynamics and exercise capacity (6MW) in patients with SSc-spectrum and normal resting PAP but exercise PH. These improvements included a significant decrease in exercise PVR, total pulmonary resistance, and mPAP, and an increase in CO and SV. The clinical significance of these observations needs to be validated by a larger placebo controlled randomized study.

Further work defining normal versus abnormal ΔPAP/ΔCO specifically for patients with scleroderma, with and without interstitial lung disease, needs to be conducted. Nonetheless, an exercise evaluation of scleroderma-PH patients may allow earlier diagnosis, earlier initiation of therapy, and perhaps a more favorable outcome.

Valvular Heart Disease

PH at rest and exaggerated during recumbent exercise testing is associated with an adverse outcome in patients with aortic and mitral valvular disease. The presence of PH at rest or during exercise should therefore be included in perioperative risk assessment of mitral and aortic valve replacement. In older patients with severe mitral valve stenosis and PH, the perioperative mortality increases to 20%; therefore, the indication of valve surgery has to be proven carefully. Preoperative PH was also an independent risk factor for long-term survival in patients with aortic valve replacement. Patients with valvular disease and normal or mildly elevated PASP at rest may develop severe PH during exercise, which may be unrelated to the resting pressure. The level of increase in PASP depends on the ability to successfully recruit the pulmonary vasculature to accommodate increased blood flow with exercise, the contribution (or proportion) of the reduction in cross-sectional area of the pulmonary circulation, the reduction in pulmonary vascular compliance, and the increase in LAP, each of which may be abnormal at rest.

Mitrail Valve Disease

Although the number of studies of exercise in mitral valve disease is limited, they consistently demonstrate that exercise-induced PH is associated with a poor outcome. Functional mitral regurgitation secondary to chronic LV dysfunction is associated with dynamic changes in PASP (as estimated by the transtricuspid pressure gradient) during exercise, and there is a correlation between the rise in PASP during exercise and the increase in mitral regurgitation. The increase in PASP is more pronounced in patients with exercise-limiting dyspnea and in those hospitalized for acute pulmonary edema, and the acute increase in PASP during exercise independently predicts cardiac death and heart failure admission. The optimal cut point for predicting an increase in cardiac events was a 21-mm Hg increase in PASP. Considering the adverse prognostic implications of exercise-induced changes in mitral regurgitation, for patients with moderate functional mitral regurgitation in whom surgical coronary revascularization is planned, an exaggerated increase in mitral regurgitation, PASP, and dyspnea during exercise echocardiography may aid in the decision of whether to include mitral valve intervention. The PASP increases markedly during exercise in a large proportion (46%) of patients with asymptomatic degenerative mitral regurgitation (prolapse or flail), and the change in PASP correlates with the change in effective regurgitant orifice and regurgitant volume. In this cohort, development of PH during exercise is associated with a 3-fold increased risk of developing symptoms at 3 years, whereas resting PH was not an independent predictor of outcome. The best cutoff value of PASP during exercise for predicting events was 56 mmHg. Although there are no prospective prognostic data, a similar threshold of PASP with exercise (>60 mmHg) has been recommended by the American College of Cardiology/American Heart Association guidelines for mitral valve intervention in patients with asymptomatic moderate to severe mitral stenosis (Class IIa indication; Level of Evidence, C), a recommendation not supported in the more recent European Society of Cardiology guidelines.

Aortic Valve Disease

A resting PASP >50 mmHg is present in ≈6% of asymptomatic patients with severe aortic stenosis. This suggests that the impact of severe aortic stenosis on LV diastolic function and left atrial geometry and function may generally be counterbalanced effectively by increasing left atrial compliance and pulmonary vasodilator reserve. Using the definition of exercise PH as a PASP >60 mm Hg, Lancellotti et al recently reported that exercise PH is frequent (55% of the cohort) in the elderly with asymptomatic severe aortic stenosis (aortic valve area <0.6 cm^2/m^2) and preserved LV ejection fraction. The rise in PASP was determined predominantly by the degrees of LV relaxation and left atrial compliance. For a given increase in LV filling
pressure, patients with smaller changes in left atrial dimensions (ie, exhausted left atrial compliance reserve) during exercise displayed a higher increase in PASP during exercise; this relationship was even stronger as recruitable left atrial function diminished, consistent with reduced atrial emptying associated with reduced left atrial function. Most important, exercise PH in asymptomatic severe AS was associated with an alarming rate of cardiac death (12%) and reduced overall 3-year cardiac event-free survival (22±7% versus 55±9%; P=0.014), and exercise PH was an independent predictor of cardiac events.63

Chronic Obstructive Lung Disease
The prevalence of PH (defined as echo Doppler PASP >35 mm Hg or mPAP >20 mm Hg on right heart catheterization) ranges between 30% and 70% in COPD (group 3 PH).64 PH in COPD is highly correlated with a decrease in functional capacity and mortality. A close relationship exists between the severity of hypoxemia and mPAP and PVR in COPD, suggesting that alveolar hypoxia causes constriction of the resistance vessels and over time induces pulmonary vascular remodeling. However, severe PH (mPAP >35-40 mm Hg) occurs in <5% of persons with COPD and typically is associated with less severe obstruction, more hypoxemia and hypocapnia, and lower Dlco.64 The latter is characterized as disproportionate or out-of-proportion PH. In a series of COPD patients with an mPAP ≥40 mm Hg, 60% were related to other associated conditions, including appetite suppressants, collagen vascular disease, portal hypertension, LV disease, chronic thromboembolic PH, and obstructive sleep apnea.45 In the middle-aged and elderly, a greater extent of emphysema on computed tomography scanning and more severe air-flow obstruction are linearly related to impaired LV filling, reduced stroke volume, and lower CO without changes in the ejection fraction.66 In addition, a low forced expiratory volume in the first second of expiration (FEV1) and obstructive airway disease are associated with a 2- to 3-fold long-term (15-year) risk of incident heart failure in middle-aged men and women.67 Thus, in COPD, it is highly likely LV diastolic dysfunction is a contributor to reduced exercise capacity and PH at rest and/or during exercise.

Patients with COPD whose exercising mPA is >30 mm Hg are more prone to develop resting PH (mean, 6 years) compared with patients whose exercising mPA is within normal limits.68 An exercise study was conducted in 98 COPD patients with resting PH (27% with ≥25 mm Hg) and without resting PH (73% with <25 mm Hg) and no LV dysfunction or comorbidities. The prevalence of PH was 5%, 27%, and 53% in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages II, III, and IV, respectively.28 Exercise resulted in an abnormal hemodynamic response (defined as ΔmPAP/ΔCO >3 mm Hg·L⁻¹·min⁻¹) in the resting PH group, ΔmPAP/ΔCO 7.1±2.88 mm Hg·L⁻¹·min⁻¹, as well as in the no PH group, ΔmPAP/ΔCO 4.55±3.33 mm Hg·L⁻¹·min⁻¹. Similar results were obtained in both groups for ΔmPAP/Δwatts. These results support that the exercise-induced rise in mPAP should be interpreted relative to the increase in CO or possibly watts, rather than relying on single absolute value of mPAP. However, caution is needed in the evaluation of mPAP/CO slope in COPD because intrathoracic pressure is more positive than negative during exercise in COPD.

Conclusions and Future Directions
There is growing evidence that measurement of mPAP during dynamic exercise provides valuable incremental information to resting hemodynamic measurements alone. Recent studies have established that an exaggerated increment in mPAP during exercise is closely associated with impaired functional capacity in HF,11 PAH,12,46 exercise-induced PH,12 and valvular heart disease.77,62 Additional recent studies have shown that exercise PAH responses potently predict adverse outcomes in HF11 and valvular heart disease55,60,62,63 and also predict future PH progression in patients with COPD.68 However, studies to date have been conducted in relatively small cohorts, using heterogenous exercise protocols, measurement methods, and definitions of abnormal hemodynamic responses to exercise.

From the studies summarized here, we conclude that ideally multipoint assessments of mPAP relative to CO should be performed during dynamic exercise, with an mPAP/CO slope >3 mm Hg·L⁻¹·min⁻¹ signaling an abnormal pulmonary vascular response to exercise. Determination of LAP or PCWP during exercise is also important to ascertain precapillary and post-capillary contributions to mPAP during exercise, but optimal cut points for abnormal exercise LAP or PCWP have not been defined.69 Future investigations are needed to further validate noninvasive methods for the evaluation of the RV and pulmonary vasculature during exercise and to further define the functional and prognostic significance of PAP-Q responses to exercise in various cardiopulmonary diseases. Finally, understanding the natural history of abnormal exercise P-Q responses and their modifiability with interventions (ie, oxygen therapy, exercise training, pulmonary vasodilators) will help determine whether exercise hemodynamic measurements can be used to diagnose early forms of PH and to inform the selection of targeted interventions.

Disclosures
None.

References
Pulmonary Vascular Responses to Exercise

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