What Is the Utility of Evaluating Patients for Exercise-Induced Pulmonary Hypertension?

Section Editor Sean M. Studer, MD, MSc Steven Hsu, MD Division of Cardiology, Department of Medicine The Johns Hopkins School of Medicine Baltimore, MD

Brian A. Houston, MD Division of Cardiology, Department of Medicine The Johns Hopkins School of Medicine Baltimore, MD

Ryan J. Tedford, MD Division of Cardiology, Department of Medicine The Johns Hopkins School of Medicine Baltimore, MD

EXERCISE-INDUCED PULMONARY HYPERTENSION

Pulmonary hypertension (PH) is currently defined by a resting mean pulmonary artery pressure (mPAP) that is \geq 25 mm Hg.¹ Prior to 2009, the definition of PH also included those with mPAP \geq 30 mm Hg with exercise, while the diagnosis of exercise-induced PH was made by observing a normal resting mPAP that increased to >30 mm Hg with exercise.²

Kovacs et al, however, demonstrated in 2009 that exercised-induced increases in mPAP occurred naturally with age.³ In their pooled analysis of 1187 *healthy* individuals from 47 different studies, patients over the age of 50 years had an average mPAP with exercise near 30 mm Hg. These data, coupled with uncertainty regarding the proper type, posture, or intensity of exercise necessary for diagnosis, led to the removal of exerciserelated definitions from the PH guidelines in 2009.⁴

Nonetheless, exercise-related changes in mPAP may have potential utility. This update will focus on recent studies illuminating pitfalls in the performance and interpretation of exercise hemodynamics and the current data supporting their clinical and diagnostic potential.

DETERMINANTS OF mPAP AND ITS NORMAL RESPONSE TO EXERCISE

Before defining a pathologic increase in mPAP, it is important to review the factors that determine mPAP, as well as the normal response of mPAP to exercise. mPAP is a function of the product of pulmonary vascular resistance (PVR) and cardiac output (CO), as well as downstream left heart pressure (estimated by pulmonary artery wedge pressure (PAWP):

 $mPAP = (PVR \times CO) + PAWP$

Pressure must always be considered in the context of flow, or CO, since mPAP will rise with increases in CO. In the normal exercising individual, an increase in CO is accompanied by a fall in PVR. This is due to a combination of pulmonary vascular recruitment and distension of the pulmonary resistance vessels.⁵ With significant pulmonary vascular pathology, however, PVR may only minimally decrease or even increase, leading to a rise in mPAP.

By examining pressure-flow relationships from available data in healthy individuals, Naeije, Lewis, and colleagues proposed that the slope of the mPAP/CO relationship should be no greater than 3 mm Hg/(L/min).⁵ Although there is some curvilinearity to the mPAP-CO relationship, it can generally be approximated as linear, especially when measures are taken at multiple time points during exercise.

Notably, while the mPAP/CO slope is useful to define abnormal vs normal responses, it cannot differentiate if a rise in mPAP is due to a failure of PVR to fall or a rising PAWP from left heart disease. In addition, the PAWP must be carefully measured during exercise, since an abnormal escalation in PAWP may lead to exercise-induced increases in mPAP,⁵ as PAWP rises normally in response to exercise. Indeed, studies of healthy individuals have shed light on the normal physiologic response by demonstrating that exercise can lead to increases in PAWP of 10 mm Hg or more in some cases.⁶⁻⁹ Upright exercise leads to PAWP values that are approximately 5 mm Hg less, on average, than those seen with supine exercise, although the absolute change in PAWP is similar.7 Based on these findings, we

Correspondence: Ryan.Tedford@jhmi.edu

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-24 via free access

consider an abnormal PAWP to be ≥ 25 mm Hg with supine exercise or ≥ 20 mm Hg with upright exercise. Because right atrial pressure (RAP) approximates pericardial pressure in most situations, examining the transmural left ventricular (LV) filling pressure (PAWP – RAP) may also be useful to tease out the component of PAWP elevation that is related to LV pathology rather than pericardial constraint.¹⁰

MEASURING EXERCISE HEMODYNAMICS

There are several important considerations to ensure proper data collection when performing exercise hemodynamic measurements. First, care must be taken to ensure proper transducer leveling, especially if upright exercise is used. Bicycle exercise is preferred to upper extremity exercise to avoid unwanted increases in systemic vascular resistance. Of course, indirect or modified Fick cardiac output estimations (which assume fixed oxygen consumption) cannot be used during exercise, as oxygen consumption increases during exertion. Although there are few data comparing thermodilution cardiac output (TDCO) to direct Fick measurements (direct measures of oxygen consumption) during exercise,^{11,12} the latter is generally preferable and has been used in most studies examining exercise hemodynamics.^{2,8,9,13-15} Furthermore, unless a high-fidelity catheter is being used, mPAP, rather than pulmonary artery systolic and diastolic pressures, should be reported due to excessive catheter ringing and motion artifact that is usually present during exercise measurements.16

Because exercise can lead to dramatic swings in intrathoracic pressure, measuring end-expiratory pressures may overestimate true pressure, especially in the setting of lung disease. Boerrigter et al recently showed that averaging pressures over the full respiratory cycle during exercise more closely approximated true pressures (confirmed by direct esophageal pressure measurements) in patients with severe obstructive lung disease.¹³ Although we do not yet have similar studies in patients without lung disease, averaging values over the entire Table 1. Potential Clinical Scenarios for the Use of Exercise-Induced Hemodynamics

	Clinical Scenario
1.	Differentiating Group 1 and 2 PH
2.	Identifying Occult Left Heart Disease, or "Early HFpEF"
3.	Identifying Exercise-Induced PAH
4.	Assessing RV Contractile Reserve

PH = pulmonary hypertension; HFpEF = heart failure with preserved ejection fraction; PAH = pulmonary arterial hypertension; RV = right ventricle

respiratory cycle is considered the pre-ferred method. $^{\rm 16}$

THE USE OF EXERCISE-INDUCED INCREASES IN MPAP AND PAWP

When reliably and accurately measured, we believe exercise-induced changes in mPAP and PAWP may be useful in at least 4 clinical scenarios: (1) differentiating Group 1 PH from Group 2 PH, (2) identifying occult but symptomatic left heart disease, (3) identifying symptomatic exercise-induced pulmonary arterial hypertension (PAH), and (4) assessing right ventricular (RV) contractile reserve (Table 1).

Differentiating Between PAH (WHO Group 1) From PH Due to Left Heart Disease (WHO Group 2)

Because treatment approaches are dramatically different, accurately categorizing a PH patient into the correct WHO diagnostic group is of paramount importance. Group 2 PH, or PH due to left heart disease, can be distinguished from Group 1 PAH by a resting PAWP or left ventricular enddiastolic pressure (LVEDP) of >15 mm Hg. Identifying Group 2 PH is relatively straightforward when reduced left ventricular ejection fraction (HFrEF) or significant valvular disease is present.¹⁷ However, Group 2 PH due to heart failure with preserved ejection fraction (HFpEF-PH) can be more difficult to identify due to the lack of ostensible left heart disease.¹⁰ Furthermore, in patients with HFpEF-PH, prior treatment with diuretics or vasodilators or even prolonged nil per os (NPO) status can lower resting PAWP into the normal range.

When resting hemodynamic investigations lead to clinical equipoise between Group 1 PH and HFpEF-PH, clinical characteristics and echocardiographic parameters may be useful to assist in diagnosis.18 When still unclear, hemodynamic assessment with exercise to elicit pathologic increases in PAWP can help support the diagnosis of HFpEF-PH.^{1,19} While saline boluses have also been used to diagnose occult HFpEF, it was recently suggested that exercise may lead to more dramatic increases in PAWP compared to saline, and therefore be more sensitive for the detection of HFpEF.^{9,19} That said, an important caveat of this study was that exercise pressures were measured at endexpiration.

Identifying Occult But Symptomatic Left Heart Disease

In 2010, Borlaug and colleagues found exercise measurements to be helpful in the diagnosis of occult left heart disease, or what they termed "early HFpEF."14 In these patients, it is thought that worsening diastolic reserve leads to symptoms and hemodynamic changes with exertion but not at rest. The group retrospectively reviewed hemodynamic data of patients being evaluated for unexplained dyspnea who had normal LV ejection fraction (\geq 50%), normal resting hemodynamics, normal B-natriuretic peptide levels, and no obvious left heart or pulmonary disease. Supine exercise PAWP $\geq 25 \text{ mm Hg}$ was used to differentiate "early HFpEF" patients from those with noncardiac dyspnea. Exercised-induced increases in pulmonary artery systolic pressure $(PASP) \ge 45 \text{ mm Hg also correlated}$ well with exercise PAWP and predicted early HFpEF with 96% sensitivity and 95% specificity. These patients also demonstrated impaired heart rate, cardiac index, and systemic vascular resistance responses characteristic of more advanced HFpEF patients.14

Identifying Exercise-Induced PAH

As described above, exercise-induced PAH previously referred to the patient with normal mPAP at rest but \geq 30 mm Hg with exercise with a normal PAWP response.¹ While some believed this to

Downloaded from https://prime-pdf-watermark.prime-prod.pubfactory.com/ at 2025-06-24 via free access

be an early phase of PAH, others considered this a stable variant.²⁰⁻²² In favor of the former hypothesis, exerciseinduced increases in mPAP >30 mm Hg have been shown to be associated with dyspnea and fatigue symptoms.²³ It has also been shown that some patients with PAH demonstrate exercise-induced elevations in mPAP that precede resting elevations in mPAP.²¹

Tolle and colleagues sought to characterize this group of patients in 2008 by retrospectively reviewing 3 years of invasive hemodynamic exercise data in patients with exertional dyspnea.² They found that patients with exercise-induced increases in mPAP >30 mm Hg (PAWP <20 mm Hg) exhibited a hemodynamic profile that was intermediate between those of normal patients and resting PAH patients (in terms of maximal oxygen consumption [VO₂max; % predicted], CO_{max}[% predicted], RV ejection fraction, alveolar-arterial difference, and PVR). Examining the relationship between exercise mPAP and VO₂ revealed 2 distinct patterns: 1) a "takeoff" pattern where mPAP rose most significantly during late exercise, possibly related to vasoconstriction; and 2) a "plateau pattern" where mPAP failed to rise with increasing VO₂, possibly indicative of RV dysfunction or worsening tricuspid regurgitation. The takeoff pattern was seen in most normal patients, whereas the plateau was more commonly seen in those with PAH. Not surprisingly, the plateau pattern was associated with reduced maximum exercise work, peak VO₂, and CO. Longitudinal data were not available in this study, nor was information on the more recently proposed mPAP/CO slope.²

Identification of exercised-induced PAH may categorize a group of patients responsive to early treatment. A small, single-centered, prospective pilot study was performed using the endothelinantagonist ambrisentan (Letairis, Gilead Sciences) to treat exercise-induced PAH associated with systemic sclerosis (SSc).²⁴ In the 11 patients that completed the 24-week study, there were significant improvements in mean PVR with exercise, 6-minute walk distance, exercise CO, mPAP, and total pulmonary resistance.²⁴ Bosentan (Tracleer, Actelion Pharmaceuticals) was also studied in 2 pilot studies—one of 10 patients and one case report of a single patient—and was found to improve hemodynamic parameters in patients with SScassociated exercise-induced PAH.^{25,26}

It should be noted that therapeutic studies using the newly proposed definition of exercise-induced PAH (mPAP/CO slope >3 mm Hg/L/min) in the setting of a normal PAWP response have not been performed. Until such studies are performed and more supporting data are available, treating exercise-induced PAH would be premature.

Assessing RV Contractile Reserve Exercise-induced changes in mPAP and RV function (RV contractile reserve) may be useful to predict prognosis in PH as well as identify patients with "hidden" RV failure. Blumberg et al found that in patients with PAH or inoperable chronic thromboembolic pulmonary hypertension (CTEPH), peak cardiac index attained with exercise correlated with peak VO₂ and, along with the mPAP/CO slope, was one of the only hemodynamic variables that predicted mortality.27 In another provocative study, 124 patients with confirmed PAH or inoperable CTEPH underwent exercise-stress Doppler echocardiography and cardiopulmonary testing, and were then prospectively followed for a mean of 3.0 years. Along with peak VO_2 , an inability to augment PASP during exercise (increase <30 mm Hg) predicted worse survival when compared to a more robust increase in PASP (>30 mm Hg) with exercise.28

Identifying a patient with "hidden" or subclinical right heart failure could have important implications for early PH treatment strategies as well as for LV assist device implantation in heart failure patients.²⁹ Measuring coupling between RV contractility and pulmonary arterial (PA) load is the gold standard for assessment of RV function and may detect abnormalities even when other clinical measures are normal.³⁰ RV-PA coupling, however, is difficult to measure clinically. In an animal model of PAH, RV reserve closely correlated with resting RV-RA coupling, suggesting that RV reserve may be a useful surrogate.³¹

Several studies have looked at RV reserve in PH patients. Recently, Claessen et al found that patients with CTEPH after pulmonary endarterectomy demonstrated a reduced peak CO, reduced VO_2 , and elevated mPAP/CO slope with exercise, despite having normal resting parameters.15 This impaired RV reserve was also seen by Bonderman and colleagues in a study of CTEPH patients with persistent exercise limitation after endarterectomy.³² While these studies focused on CTEPH, the use of exercise evaluation to determine RV contractile reserve will likely play an important role in many categories of PH.

CONCLUSION

Although removed from the formal definition of PH in 2009, exercise-induced changes in mPAP and PAWP do occur and can be useful if properly performed. Although we believe additional work is needed before exercise-induced PAH is reintroduced to the guidelines, there are several clinical scenarios in which assessing exercise hemodynamics may be helpful. These include differentiating between Group 1 and 2 PH, identifying occult or early stage HFpEF, identifying exercise-induced PAH, and assessing RV contractile reserve and prognosis in patients with known PH.

References

1. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol.* 2013;62(25 Suppl): D42-D50.

2. Tolle JJ, Waxman AB, Van Horn TL, Pappagianopoulos PP, Systrom DM. Exercise-induced pulmonary arterial hypertension. *Circulation*. 2008; 118(21):2183-2189.

3. Kovacs G, Berghold A, Scheidl S, Olschewski H. Pulmonary arterial pressure during rest and exercise in healthy subjects: a systematic review. *Eur Respir J.* 2009;34(4):888-894.

4. Badesch DB, Champion HC, Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;54(1 Suppl): S55-S66.

5. Nacije R, Vanderpool R, Dhakal BP, et al. Exercise-induced pulmonary hypertension: physiological basis and methodological concerns. *Am J Respir Crit Care Med.* 2013;187(6):576-583.

6. Bevegard S, Holmgren A, Jonsson B. Circulatory studies in well trained athletes at rest and during heavy exercise. With special reference to stroke volume and the influence of body position. *Acta Physiol Scand.* 1963;57:26-50.

 Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. *Am J Cardiol.* 1978;41(1): 52-59.

8. Lewis GD, Murphy RM, Shah RV, et al. Pulmonary vascular response patterns during exercise in left ventricular systolic dysfunction predict exercise capacity and outcomes. *Circ Heart Fail*. 2011;4(3):276-285.

9. Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Cir Heart Fail.* 2015;8(1):41-48.

10. Borlaug BA. Invasive assessment of pulmonary hypertension: time for a more fluid approach? *Cir Heart Fail*. 2014;7(1):2-4.

11. Kubo SH, Burchenal JE, Cody RJ. Comparison of direct Fick and thermodilution cardiac output techniques at high flow rates. *Am J Cardiol.* 1987;59(4):384-386.

12. Lipkin DP, Poole-Wilson PA. Measurement of cardiac output during exercise by the thermodilution and direct Fick techniques in patients with chronic congestive heart failure. *Am J Cardiol.* 1985;56(4):321-324.

13. Boerrigter BG, Waxman AB, Westerhof N, Vonk-Noordegraaf A, Systrom DM. Measuring central pulmonary pressures during exercise in COPD: how to cope with respiratory effects. *Eur Respir J.* 2014;43(5):1316-1325.

14. Borlaug BA, Nishimura RA, Sorajja P, Lam CS, Redfield MM. Exercise hemodynamics enhance diagnosis of early heart failure with preserved ejection fraction. *Circ Heart Fail.* 2010;3(5): 588-595.

15. Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary

vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. *J Am Heart Assoc.* 2015; 4(3):e001602.

16. Lewis GD, Bossone E, Naeije R, et al. Pulmonary vascular hemodynamic response to exercise in cardiopulmonary diseases. *Circulation*. 2013; 128(13):1470-1479.

17. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation*. 2012; 126(8):975-990.

18. Thenappan T, Shah SJ, Gomberg-Maitland M, et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2011;4(3): 257-265.

19. Robbins IM, Hemnes AR, Pugh ME, et al. High prevalence of occult pulmonary venous hypertension revealed by fluid challenge in pulmonary hypertension. *Circ Heart Fail.* 2014;7(1): 116-122.

20. Proudman SM, Stevens WM, Sahhar J, Celermajer D. Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. *Intern Med J.* 2007;37(7):485-494.

21. Raeside DA, Chalmers G, Clelland J, Madhok R, Peacock AJ. Pulmonary artery pressure variation in patients with connective tissue disease: 24 hour ambulatory pulmonary artery pressure monitoring. *Thorax.* 1998;53(10):857-862.

22. McGoon M, Gutterman D, Steen V, et al; American College of Chest Physicians. Screening, early detection, and diagnosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(1 Suppl): 14S-34S.

23. Bossone E, Naeije R. Exercise-induced pulmonary hypertension. *Heart Fail Clin.* 2012;8(3): 485-495.

24. Saggar R, Khanna D, Shapiro S, et al. Brief report: effect of ambrisentan treatment on exercise-

induced pulmonary hypertension in systemic sclerosis: a prospective single-center, open-label pilot study. *Arthritis Rheum*. 2012;64(12):4072-4077.

25. Yagi S, Akaike M, Iwase T, et al. Bosentan ameliorated exercise-induced pulmonary arterial hypertension complicated with systemic sclerosis. *Intern Med.* 2010;49(21):2309-2312.

26. Kovacs G, Maier R, Aberer E, et al. Pulmonary arterial hypertension therapy may be safe and effective in patients with systemic sclerosis and borderline pulmonary artery pressure. *Arthritis Rheum.* 2012;64(4):1257-1262.

27. Blumberg FC, Arzt M, Lange T, Schroll S, Pfeifer M, Wensel R. Impact of right ventricular reserve on exercise capacity and survival in patients with pulmonary hypertension. *Eur J Heart Fail.* 2013;15(7):771-775.

28. Grünig E, Tiede H, Enyimayew EO, et al. Assessment and prognostic relevance of right ventricular contractile reserve in patients with severe pulmonary hypertension. *Circulation*. 2013;128(18): 2005-2015.

29. Houston BA, Tedford RJ. Stressing the stepchild: assessing right ventricular contractile reserve in pulmonary arterial hypertension. *Eur Respir J.* 2015;45(3):604-607.

30. Tedford RJ, Mudd JO, Girgis RE, et al. Right ventricular dysfunction in systemic sclerosisassociated pulmonary arterial hypertension. *Circ Heart Fail.* 2013;6(5):953-963.

31. Guihaire J, Haddad F, Noly PE, et al. Right ventricular reserve in a piglet model of chronic pulmonary hypertension. *Eur Respir J.* 2015;45(3): 709-717.

32. Bonderman D, Martischnig AM, Vonbank K, et al. Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. *Chest.* 2011;139(1): 122-127.