

Pulmonary Vascular Response Patterns to Exercise: Is There a Role for Pulmonary Arterial Pressure Assessment During Exercise in the Post-Dana Point Era?



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Pulmonary hypertension (PH) is often diagnosed late in its course when it purports a particularly poor prognosis. Exercise effectively unmasks early forms of several cardiopulmonary diseases but the role of performing pulmonary arterial pressure measurements during exercise in the evaluation of PH remains unclear. Whether pulmonary arterial pressure-flow relationships during exercise may provide a window into earlier diagnosis of functionally significant pulmonary arterial hypertension and left ventricular dysfunction or add incrementally to our armamentarium of diagnostic tests and prognostic indicators in PH is the topic of active ongoing investigation. Evidence is emerging that abnormal pulmonary arterial pressure response patterns to exercise, when properly indexed to increased blood flow, may help to identify early forms of heart failure and pulmonary arterial hypertension. This article will discuss approaches to performing hemodynamic measurements during exercise as well as the potential clinical utility of identifying normal and abnormal pulmonary vascular response patterns to exercise.

Pulmonary arterial pressure (PAP) responses to exercise were first characterized over 60 years ago,⁴ yet uncertainties remain about the role of performing exercise PAP measurements in the evaluation and treatment of pulmonary hypertension (PH). Pulmonary hypertension was previously defined in United States and European guidelines as a mean PAP (mPAP) >25 mm Hg at rest or >30 mm Hg during exercise.^{5,6} In 2008 the Working Group on Diagnosis and Assessment of Pulmonary Arterial Hypertension from the Fourth World Symposium on PH (Dana Point, CA) appropriately concluded that mPAP >30 mm Hg should be abandoned as a diagnostic criteria for PH. This decision was based on the age-dependent nature of exercise mPAP⁷ and limited data on normal subjects derived from heterogeneous levels, types, and postures during exercise testing.⁸

Exercise does, however, remain a highly relevant physiologic stressor in patients with PH. Exercise probes the reserve capacity of the right ventricular (RV)-pulmonary vascular unit to accommodate increased blood flow. Exertional dyspnea is the most common symptom that leads to the diagnosis of PH and exercise capacity predicts prognosis and characterizes responses the therapies in PH. Moreover, resting mPAP does not

closely correlate with symptoms or exercise capacity. Whether exercise hemodynamic measurements may provide a window into earlier diagnosis of functionally significant PH and left ventricular (LV) dysfunction^{1,26} or add incrementally to our armamentarium of diagnostic tests and prognostic indicators in PH is the topic of active ongoing investigation. This article will examine the current state of knowledge of pulmonary vascular response patterns to exercise in normals and in individuals with cardiopulmonary diseases to begin to frame the role of measuring pulmonary hemodynamics in the evaluation of patients with PH.

METHODS FOR MEASUREMENT OF PULMONARY HEMODYNAMICS DURING EXERCISE

Invasive Hemodynamic Measurements During Exercise

Right heart catheterization (RHC) with invasive hemodynamic monitoring is the gold standard for evaluating the pulmonary vasculature during exercise, as it is at rest. Exercise testing with invasive hemodynamic monitoring has been successfully performed using upright and supine cycle ergometry,⁷ leg presses,^{4,12} and treadmill protocols.^{13,14} A detailed description of methods utilized in our labo-

ratory at Massachusetts General Hospital,^{15,16} where ~150 cardiopulmonary exercise studies with invasive hemodynamic measurements are performed annually, is described by Drs Oldham and Systrom in this issue of *Advances in Pulmonary Hypertension* (101–106).

Upright cycle ergometry offers the advantage of simulating upright posture employed in activities of daily living, while allowing precise continuous ramp incremental work and eliciting near maximum exercise capacity without excessive upper body movement during hemodynamic measurements. Multisite oxygen saturation measurements should be performed upon insertion of the right heart catheter if left-to-right shunting is suspected, particularly when measuring Fick cardiac outputs (CO) during exercise. High fidelity micromanometer-tipped catheters, which can be advanced via fluid filled catheters inserted for routine RHC, are preferred when available to maximize accuracy of pressure measurements. Pulmonary capillary wedge pressure (PCWP) should be verified based on characteristic waveforms, systemic oxygen saturation, and/or appearance on fluoroscopy. The critical extravascular closure pressure imposed by the lung parenchyma that contains the pulmonary vasculature is typically below that of the PCWP during exercise,^{13,17} and therefore PCWP can be used as the downstream pressure in order to determine transpulmonary pressure gradients (TPG=mPAP-PCWP) and pulmonary

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vascular resistance ($PVR = TPG/CO$). Care should be taken to maintain consistent upright posture relative to the leveled transducers throughout exercise. Serial measurements of mPAP, PCWP, and CO should be performed at regular intervals (ie, every minute) during incremental exercise to characterize pressure-flow relationships. In light of increased thoracic pressure changes with exercise, particularly in overweight or deconditioned patients, it is important to uniformly measure pressures at end-expiration, when intrathoracic pressure most closely approximates atmospheric pressure, in order to ensure consistency in data interpretation.

Assessment of exercise-induced increases in mPAP should be interpreted relative to increases in blood flow (ie, $\Delta PAP/\Delta CO$) and specific work rates rather than relying on a single absolute PAP threshold (ie, 30 mm Hg) or a peak exercise mPAP. Indexing changes in mPAP to work rate or changes in CO accounts for interindividual variability in peak exercise intensity levels achieved. Determination of relative contributions to exercise mPAP from increases in left sided hydrostatic pressure (ie, PCWP or LV end-diastolic pressure [LVEDP]) and precapillary PAP (ie, the transpulmonary gradient, [TPG]) is also critical in order to discern the etiology of exercise limitation.

Noninvasive Measurements During Exercise

Doppler echocardiography is increasingly utilized as a screening procedure for pulmonary arterial hypertension (PAH)^{18,19} and may be performed to estimate right ventricular systolic pressure (RVSP), which approximates systolic PAP (PASP) in the absence of pulmonary valve stenosis or RV outflow tract stenosis.²⁰ One report found an excellent correlation between catheter-based and echocardiographic measurements obtained simultaneously during exercise ($R=0.98$). Recently echocardiographic estimates of cardiac output and mPAP have been combined with reasonable approximation of normal exercise PAP-flow relationships in healthy individuals (Table 1).²²

However, tricuspid regurgitant velocity to estimate PASP is technically challeng-

ing to ascertain during exercise²¹ and both overestimation and underestimation of PASP have been reported to occur^{20,23,24} In addition, exercise echocardiography has limited capacity to measure LV filling pressures during exercise in order to exclude the common condition of impaired LV filling mediating pulmonary venous hypertension during exercise.^{25,26} Finally, although resting echocardiographic indices of RV structure and function play a very important role in characterizing PH, and emerging echo-based measurements such as strain-rate imaging, eccentricity, Tei indices, and TAPSE offer valuable information,²⁷ echocardiographic indices of RV function have not been widely validated during exercise. Therefore, further investigation is needed to determine if exercise echocardiography should be utilized in the evaluation of PH.

PULMONARY VASCULAR RESPONSES TO EXERCISE IN HEALTHY SUBJECTS

The relationship between PAP and blood flow during exercise in normal individuals and in patients with cardiopulmonary diseases was first reported by Drs Hickam and Cargill in 1948, and was among the first observations in human cardiac catheterization.⁴ In 8 healthy subjects (age 23 ± 7 years) undergoing low-level supine leg press exercise (~ 20 watts) they observed a modest increase in mPAP (2 ± 2 mm Hg) in the context of a 3.5 ± 2.8 L increase in CO. Subsequent studies in healthy individuals have employed various exercise modalities, postures, and protocols resulting in widely variable absolute mPAP values achieved during exercise.

A recent meta-analysis was conducted that consisted of 47 studies describing 72 populations of healthy volunteers who underwent RHC with invasive measurement of PAP at rest and during exercise.⁷ Importantly, data were stratified by sex, age, type of exercise (ie, cycle ergometry, treadmill exercise), body position (upright vs supine), and exercise levels (slight, submaximal, and maximal). Normal resting mPAP was 14 ± 3 mm Hg. The upper limit of normal (ULN) was 21 mm Hg. During slight exercise, the mean and ULN for mPAP was 21 ± 7 and 33 (supine) and

20 ± 4 and 29 mm Hg (upright). During maximal exercise, the ULN was 37 (supine) and 35 mm Hg (upright).

The size of this study permitted several important observations regarding relationships between exercise PAP and potential covariates. Age ≥ 50 years was associated with slightly higher mPAP at rest (15 ± 4 mm Hg vs 13 ± 3 mm Hg in subjects < 50 years old), and markedly higher mPAP during slight exercise (29 ± 8 vs 20 ± 5 mm Hg, $P < 0.0001$). Gender did not significantly influence resting or exercise mPAP and upright position was associated with a modest reduction in exercise mPAP and cardiac output along with increased heart rate. One limitation of this study was the lack of information about the influence of body mass index (BMI) on exercise PAP, due to the paucity of overweight and obese subjects studied. Population-based studies have indicated higher PASP in individuals with higher BMI,²⁸ suggesting that exercise PAP relative to CO is likely to be greater in obese individuals.

In comparing studies of exercise pulmonary hemodynamics derived from heterogeneous exercise protocols and intensity levels, it is helpful to index exercise-induced increases in PAP to increases in blood flow (ie, $\Delta PAP/\Delta CO$, Table 1). Linear pressure-flow relationships have been observed across a wide range of flows in isolated lung preparations,^{29,30} intact animal models,³¹ and in the majority of humans who underwent serial PAP and CO measurements during exercise (Figure 1).^{7,13,32-35} Accordingly, an average PAP increment of ~ 1 mm Hg per liter of CO in young, healthy controls was evident in high intensity exercise protocols (240-276 W),^{33,35,36} and in protocols with lower intensity exercise (~ 20 W).^{4,12,37}

Early studies of pulmonary hemodynamics during exercise often did not measure exercise PCWP to permit assessment of postcapillary, LV hydrostatic pressure contributions to increases in exercise PAP.^{4,12,14,32} Studies in which serial measurements of mPAP and PCWP were performed during upright exercise in normal young individuals indicate a greater contribution of $\Delta PCWP$ compared to ΔTPG to $\Delta mPAP$ with a ratio of approximately 2:1 (ie, $\Delta PCWP = 0.67$ mm Hg/L CO and

Table 1: Pulmonary Arterial Pressure Responses to Exercise

Condition	Author	N	Age	Exercise Protocol	Work Rate (Watts)	CO at Rest (L/min)	CO With Ex (L/min)	mPAP at Rest (mm Hg)	mPAP With Ex (mm Hg)	Δ PAP/ Δ CO
NORMAL										
	Hickam ⁴	8	23±7	Supine leg press	20±7	7.1±1.8	10.4±3.5	11±3	13±1	0.9
	Lonsdorfer ³⁶	7	31±8	Upright cycle	276±50	5.4±1.5	20.0±3.3	14±2	27±6	0.9
	Degre ³²	11	41±5	Upright cycle	NA	5.0±0.9	13.3±1.7	11±4	23±5	1.4
	Slonim ¹²	5	22±2	Supine leg press	20 ± 2	4.9±0.6	7.2±0.8	15±2	19±2	1.6
	Wagner ³³	8	30 ± 6	Upright cycle	180	6.9±2.0	20.5±2.5	13 ± 3	30±6	1.2
	Damato ¹⁴	24	31±6	Upright treadmill	160±23	5.1±0.8	17.5±2.0	15±5	29±8	1.1
	Reeves ³⁵	9		Upright cycle	240	6.7±1.2	24.7±3	15±2	29±8	0.8
	Tolle ¹	16	46±15	Upright cycle	156±43	5.8±1.0	15.5±3.2	14±3	27±4	1.4
	Argiento ²²	25	36±14	45° cycle	170±51	4.7±1.0	18.0±4.2	14±3	30±7	1.4
	Kovacs ⁷	116	>50	Supine	NA	6.2±1.5	11.2±2.0	15±4	29±8	2.8
COPD										
	Hickam ⁴	5	51±10	Supine leg press	10	6.2±1.0	7.8±2.3	18±5	25±2.5	4.0
	Saito ⁹¹	14	67±7	Supine cycle	27	4.3±0.7	8.8±1.1	19±4	41±10	4.6
COPD+PH	Blanco ⁷⁴	20	64±7	Upright cycle	NA	4.9±1.0	9.0±2.2	27±10	56±14	7.0
HEART FAILURE										
HFrEF	Lewis ¹⁵	13	47±9	Upright cycle	83±10	3.2±0.2	4.8±0.3	28±4	36±4	5.0
HFrEF	Lewis ⁶⁵	30	56±4	Upright cycle	75±11	3.5±0.3	6.8±0.4	30±3	49±3	4.9
HFrEF	Mancini ⁶⁹									
Survivors		49	53±10	Upright cycle	NA	4.0±1.1	7.7±2.1	28±11	46±12	4.9
Nonsurvivors		16	52±8			4.1±0.8	7.1±2.3	31±10	55±8	8.0
HFrEF	Janicki ¹³	42		Upright treadmill	NA	3.7±1.3	7.3±2	27±11	48±13	5.9
HFpEF	Borloug ²⁶	32	65±13	Supine cycle/arm	47±19	5.2±1.1	9.1±1.9	19±4	43±7	6.1
PAH										
	Janicki ¹³	9		Upright treadmill	NA	3.4±0.7	8.9±2.7	43±16	81±16	6.1
	Blumberg ⁶⁰	16	55±8	45° cycle	25-50	3.7±1	5.8±2.4	45±8	70±13	11.9

CO indicates cardiac output; mPAP indicates mean pulmonary arterial pressure; Δ PAP/ Δ CO indicates the slope of the pulmonary arterial pressure-flow relationship during exercise; COPD indicates chronic obstructive pulmonary disease; HFrEF indicates heart failure with reduced ejection fraction; HFpEF indicates heart failure with preserved ejection fraction.

Δ TPG=0.33 mm Hg/L CO).³³⁻³⁵ Older individuals have greater augmentation in mPAP relative to blood flow during exercise but similar relative contributions of changes in TPG and PCWP to changes in mPAP during exercise.⁷ The modest increment in TPG relative to CO during exercise results in a reduction in PVR to less than 1 Wood unit. The reduction in PVR with exercise is attributable to passive recruitment and distention of a compliant pulmonary circulation and active flow-mediated vasodilation.^{38,39}

From investigations to date in normal individuals, it can be concluded that the compliant pulmonary vasculature can accommodate large increases in blood flow during exercise with a proportionate mod-

est increment in mPAP and a fall in PVR. When assessing mPAP, it is critical to account for CO augmentation; therefore, determination of Δ mPAP/ Δ CO or PVR is preferable to mPAP alone.

EXERCISE HEMODYNAMIC MEASUREMENTS TO UNMASK EARLY FORMS OF PAH AND LV DYSFUNCTION

When advanced, heart failure with preserved ejection fraction (HFpEF) and PAH are readily apparent through routine clinical evaluation and diagnostic testing performed at rest. However, the diagnosis of earlier stages of HFpEF and PAH may be challenging, as exertional dyspnea is not specific for either condition, and biomarkers and he-

modynamic indicators in “early stages” of these conditions may be unremarkable at rest.²⁶ Therefore, individuals who experience dyspnea on exertion despite normal resting hemodynamics (ie, PCWP or LVEDP <15 mm Hg⁴⁰ and mPAP <25 mm Hg) may benefit from confrontational testing with exercise with particular attention to relative increases in PCWP and TPG components of PAP.

Exercise-induced Heart Failure With Preserved Left Ventricular Ejection Fraction

HFpEF constitutes approximately 40% of the HF population and is associated with a similar prognosis to HF with reduced LV ejection fraction (LVEF).⁴¹ 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 The potential for over-diagnosis of HFpEF based on these criteria has garnered significant attention⁴³⁻⁴⁵ but less is known about the potential under-diagnosis of HFpEF in symptomatic patients without overt hypervolemia.

Borlaug et al reported hemodynamic responses to exercise in 55 euvoletic subjects with exertional dyspnea, normal natriuretic peptide levels, and normal resting hemodynamic measurements.²⁶ Supine exercise with cycle ergometry (N=42) or arm weights (N=13) was performed, with an exercise PCWP threshold of ≥ 25 mm Hg for the diagnosis of HFpEF. This PCWP value was chosen based on previous studies in normal controls showing that peak PCWP and LVEDP during supine exercise are <20 - 23 mm Hg^{46,47} and <25 mm Hg,⁴⁸ respectively. HFpEF subjects experienced significantly greater exercise-induced increases in mPAP (ie, from 19 ± 4 to 43 ± 7 mm Hg) compared to subjects with noncardiac dyspnea (ie, from 15 ± 4 to 23 ± 5 mm Hg, Figure 2A) despite achieving lower peak COs. Exaggerated increases in mPAP in HFpEF were related exclusively to elevations in exercise PCWP as evidenced by similar increments in TPG and reductions in PVR from rest to exercise in HFpEF and noncardiac dyspnea patients. Exercise-induced changes in PCWP and PAP in patients with HFpEF remained significantly higher than those in patients with noncardiac dyspnea following adjustment for age, BMI, CO, and work rate.

Borlaug and colleagues further examined the discriminatory capacity of exercise PAP for the diagnosis of HFpEF. They focused on exercise PASP because it was closely related to exercise PCWP ($R=0.76$, $P<0.0001$) and is amenable to noninvasive estimation by echo Doppler. $PASP >45$ mm Hg identified HFpEF with 96% sensitivity and 95% specificity (Figure 2B). Strict exclusion of patients with pulmonary vascular disease (ie, mPAP >25 mm Hg at rest or

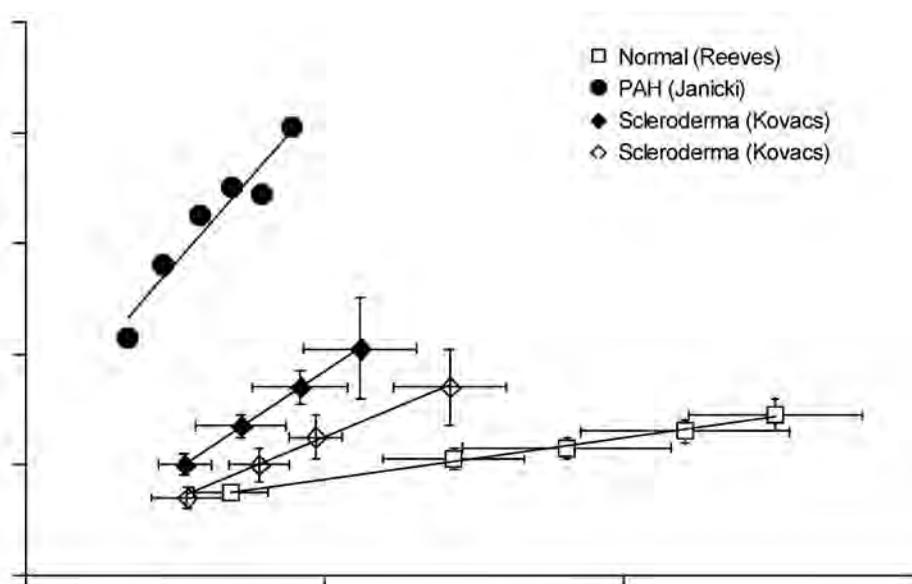


Figure 1: Pulmonary arterial pressure (PAP)-flow relationships based on serial measurements of mean PAP and cardiac output during incremental exercise. Normal subjects (\square), patients with scleroderma with PAP in the lower normal range (\diamond) and upper normal range (\blacklozenge), and patients with resting PAH (\bullet) demonstrate approximately linear pressure-flow responses during exercise. Higher $\Delta PAP/\Delta CO$ than normal may be indicative of early pulmonary vasculopathy in the scleroderma groups. Data from (\square) Reeves,³⁵ Kovacs (\diamond, \blacklozenge),⁵⁴ and (\bullet) Janicki.¹³

>30 mm Hg during exercise with a PCWP <15 mm Hg) likely inflated the specificity of exercise PASP for the diagnosis of HFpEF, compared to an unselected population of patients with exertional dyspnea, but exercise PASP outperformed resting PASP, natriuretic peptide levels, and echocardiographic indicators for diagnosing HFpEF.

Kitzman et al similarly found 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.⁴⁹ Both studies indicate the incremental value of exercise hemodynamics in the diagnosis of HFpEF and may pro-

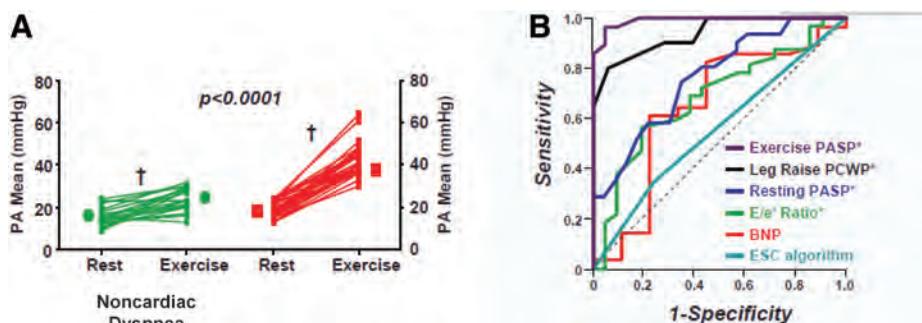


Figure 2: (Panel A) Mean PAP increased to a greater extent during exercise in patients with HFpEF compared to patients with noncardiac dyspnea. (Panel B) Clinical measures (B-type natriuretic peptide levels and echocardiographic E/e') and the European Society of Cardiology (ESC) diagnostic algorithm⁴² did not robustly distinguish HFpEF from noncardiac dyspnea. In contrast, PCWP with leg raise and exercise PASP showed excellent discrimination between HFpEF and noncardiac dyspnea. Reprinted with permission from Wolters Kluwer Health: Borlaug BA, et al. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure with Preserved Ejection Fraction. *Circ Heart Fail*. 2010 Jun 11. [Epub ahead of print]

vide a window into earlier diagnosis of the condition. However, prior to labeling elevations in exercise hemodynamics as “early forms” of HFpEF, more information is needed on the natural history of patients with exercise elevations in PAP and PCWP to determine the rate at which they go on to develop overt HF.

Exercise-induced PAH

Analogous to HFpEF, PAH is often diagnosed late in its course when it purports a particularly poor prognosis. Whether exercise-induced elevations in mPAP provide a window into the diagnosis of early, potentially more treatable forms of PAH remains controversial.^{6,50,51} Definitions of exercise-induced PAH (EIPAH) and the rigor with which pulmonary venous hypertension has been excluded in studies performed to date varies.^{1,52,53} Furthermore, follow up to determine natural history of EIPAH is lacking. However, there is emerging evidence that EIPAH, if properly defined, may represent an important intermediate PAH phenotype.^{1,54}

Tolle and colleagues conducted a comprehensive study of 406 sequential patients undergoing incremental cardiopulmonary exercise testing with invasive hemodynamic monitoring to evaluate dyspnea on exertion and thereby compiled the largest EIPAH experience reported to date. “Exercise-induced PAH” was defined as resting mPAP <25 mm Hg coupled with exercise PCWP <20 mm Hg, mPAP >30 mm Hg, and PVR >80 dyne·s·cm⁻⁵. Patients with EIPAH (N=78) were compared to patients with normal exercise capacity and hemodynamics (N=16) and patients with resting PAH (mPAP >25 mm Hg, PCWP <15 mm Hg, N=15). The inclusion of an exercise PVR minimum in the definition of EIPAH was particularly important in light of the subsequently published meta-analysis by Kovacs indicating that mPAP=30 mm Hg is often surpassed during exercise in normals performing maximum exercise,⁷ particularly when high workloads are achieved.^{33,35} In addition, a PCWP <20 mm Hg during maximum exercise³⁴ represents a relatively strict threshold to exclude a primary contribution of elevated left sided hydrostatic pressures to PH dur-

ing exercise and further helps to validate the findings from this study.

Tolle and colleagues found that the percent predicted peak VO₂ (on the basis of age, sex, and height)⁵⁵ was lowest in resting PAH (55.8%±20.3%), intermediate in EIPAH (66.5%±16.3%), and highest in normals (91.7%±13.7%), whereas mPAP (48±11 vs 37±6 vs 27±4 mm Hg) and PVR (294±158 vs 161±60 vs 62±20 dyne·s·cm⁻⁵, respectively; all *P*<0.05) followed an opposite pattern. These data suggest that EIPAH is an intermediate phenotype between normal subjects and those with resting PAH. Of note, the ULN mPAP in the upright position is likely closer to 20 mm Hg instead of 25 mm Hg, but Tolle et al noted that resting mPAP 21-25 mm Hg in this study did not predict EIPAH. The important findings of this study characterizing EIPAH merit further exploration of the natural history of EIPAH to determine its prognostic implications and responsiveness to therapy.

Subsequent studies have provided further evidence of the functional significance of exercise-induced elevations in PAP. Kovacs and colleagues studied 29 patients with systemic sclerosis, an “at-risk population” for PAH, in whom resting mPAP was <25 mm Hg. Stratification by median mPAP at rest (mPAP=17 mm Hg) and during exercise at 25 and 50 watts (median PAP=23 mm Hg and 28 mm Hg, respectively), indicated that higher resting PAP within the normal range, and particularly higher exercise PAP was associated with reduced 6-minute walk distance and reduced peak workload.⁵⁴ Notably, the PVR failed to fall in the above-median PAP, EIPAH group (rest: 168±47 dyne·s·cm⁻⁵, 25W: 161±36 dyne·s·cm⁻⁵, 50W: 166±41 dyne·s·cm⁻⁵). These values are strikingly similar to the PVR values reported by Tolle et al in EIPAH (161±60 dyne·s·cm⁻⁵). A second recent publication in patients with systemic sclerosis demonstrated the utility of exercise hemodynamics in identifying the primary mediator of potentially multifactorial exercise limitation.⁵⁶

EIPH and LV Dysfunction

The studies described above compartmentalize patients as having either HFpEF or

PAH unmasked by exercise. However, in some patients exercise will elicit exaggerated increases in both TPG and PCWP. The entity of “PH out of proportion to LV dysfunction,” alternatively named “PH-LVD” or “mixed PH,” as identified by abnormal resting hemodynamics, is being increasingly recognized in patients with both HFpEF⁵⁷ and HF with reduced LVEF (HFREF).⁵⁸ For example, Lam et al recently described a wide spectrum of PASPs in patients with HFpEF, with higher PASP potently predicting worse outcomes.^{57,59} The identification of exercise-induced mixed PH, with partitioning of relative contributions of PCWP and TPG, may help to further phenotype patients with dyspnea and eventually inform targeted interventions directed at either the left ventricle or the pulmonary vasculature.

Based on studies to date in normal individuals and in dyspneic patients in the studies described above, a suggested algorithm is proposed in Figure 3 whereby patients can be further classified on the basis of exercise hemodynamic values. The initial branch point is based on marked differences in pressure-flow relationships in the pulmonary vasculature in normals relative to individuals with HF or PAH (Table 1).

PULMONARY VASCULAR RESPONSES TO EXERCISE IN ESTABLISHED CARDIOPULMONARY DISEASES

Pulmonary Arterial Hypertension

Patients with confirmed PAH demonstrate steep pressure-flow relationships during exercise (Table 1).⁶⁰ When exercise-induced increases in PAP are analyzed relative to work rate or VO₂ during maximum incremental exercise, a plateau pattern in PAP has been observed.^{1,61} This pattern of a steep initial increment in PAP coupled with inability to augment PAP throughout exercise may be indicative of dynamic RV dysfunction. Hence, while exercise hemodynamic measurements are not necessary to confirm the diagnosis of PAH, they may aid in probing the compensatory capacity of the RV-pulmonary vascular unit.

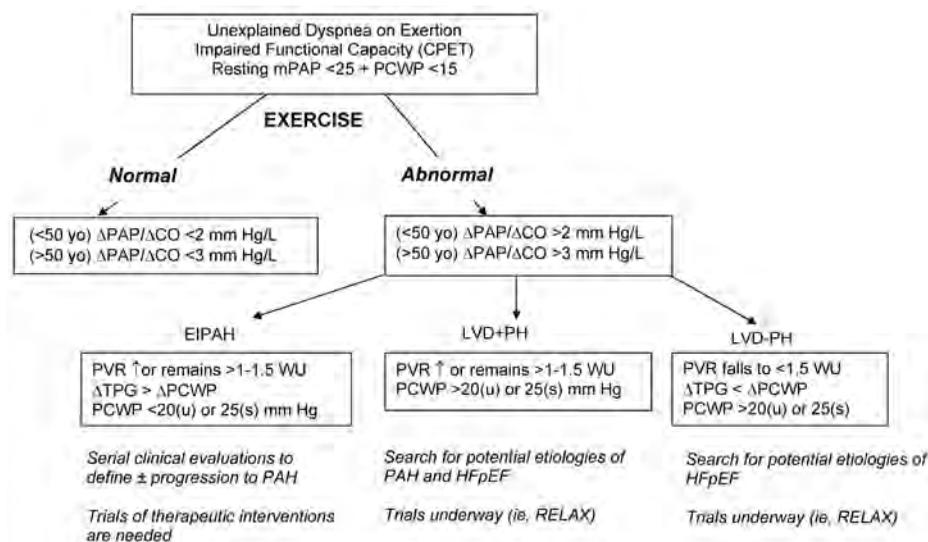


Figure 3: Diagnostic algorithm for evaluation of pulmonary vascular response patterns to exercise in the setting of normal resting filling pressures. CPET indicates cardiopulmonary exercise test. $\Delta\text{PAP}/\Delta\text{CO}$ indicates relative changes in pulmonary arterial pressure and cardiac output during exercise. WU indicates Wood units; TPG indicates transpulmonary gradient; PCWP indicates pulmonary capillary wedge pressure; (u) and (s) indicate upright and supine, respectively.

Heart Failure With Reduced LVEF

Resting PH is present in the majority of patients with LV systolic dysfunction (LVSD) and is associated with RV dysfunction, reduced exercise tolerance, and poor prognosis.^{58,62,63} There is a strong inverse relationship between resting PVR and exercise capacity as measured by peak VO_2 .^{58,64} Despite the recognized importance of resting PH and RV dysfunction in LVSD, less is known about the PAP response patterns during exercise in subjects with LVSD, and their relationship to exercise capacity and outcomes.

In our laboratory we studied 2 cohorts of subjects with LVSD who underwent cardiopulmonary exercise testing (CPET) with measurements of PAP, PCWP, and Fick CO.^{15,65} We observed an exaggerated increase in PAP relative to CO during exercise of 4.9 mm Hg/L and 5.0 mm Hg/L in 2 separate studies. Despite uniform increases in PCWP, PVR failed to fall normally with exercise, remaining in excess of 3 Wood units on average during exercise in both studies. Exercise PVR was strongly associated with 3 established prognostic indicators in HF: peak VO_2 , RV ejection fraction (RVEF), and V_E/V_{CO_2} slope.^{66,67} Janicki et al similarly

observed an increment in PAP relative to CO of 5.9 mm Hg/L¹³ in 42 subjects with HF. Notably, patients with resting mPAP <19 mm Hg, indicating well compensated HF, had an average increment in PAP of 4.1 mm Hg/L whereas those with resting mPAP >19 mm Hg had an increment in PAP of 6.8 mm Hg/L. Unlike our group, Janicki observed a modest decrement in PVR in both subgroups during exercise, but the average PVR remained above 2 Wood units during exercise.

Two studies have examined whether invasive hemodynamic measurements during exercise,^{68,69} including mPAP, provide incremental prognostic information in HFpEF. Mancini et al examined rest and exercise hemodynamics and gas exchange variables in 65 patients who underwent cardiac transplantation evaluation and stratified them into 2 groups: those who died or required urgent transplant (N=16), and those who survived (N=49) over an average follow-up of 8 ± 4 months. Nonsurvivors did not differ from survivors in resting hemodynamics, including mPAP and CO. However, during exercise nonsurvivors had higher mPAP (55 ± 8 mm Hg) than survivors (46 ± 12 mm Hg, $P=0.01$, Table 1) and

higher increment in mPAP per liter of CO (8.0 vs 4.9 mm Hg/L). In a similar study, Metra et al evaluated 219 patients (181 survivors and 38 nonsurvivors) and found that both rest and exercise PAP were higher in nonsurvivors than in survivors, despite lower workloads achieved in nonsurvivors.⁶⁸ Furthermore, exercise PVR, but not resting PVR, distinguished survivors from nonsurvivors. Both studies indicate superior prognostic value of measuring exercise pulmonary hemodynamics compared to resting measurements alone. Peak exercise mPAP, however, was not retained in multivariate analyses of predictors of survival in either study. Whether this finding was attributable to limited incremental prognostic value of exercise mPAP, failure to account for lower workloads in nonsurvivors, or to inclusion of interrelated exercise hemodynamic variables into the multivariate models (ie, stroke work index) requires further investigation.

Several mechanisms may account for the heightened mPAP/CO relationship observed in HF. Increased hydrostatic pressures during exercise due to LV dysfunction are to be expected, but persistent elevations in PVR reflect exaggerated increases in TPG during exercise as well. This may be due to maximally recruited pulmonary vasculature at rest on account of elevated resting hydrostatic pressures, thus limiting passive recruitment and distension during exercise observed in normals. Alternatively, subnormal mixed venous oxygen saturation in HF during exercise may contribute modestly to hypoxic-vasoconstriction.⁷⁰ Finally, in one echocardiographic study, PH in HFpEF was closely related to the severity of functional mitral regurgitation and diastolic dysfunction, both at rest and during exercise.^{71,72} Trials are currently underway to evaluate the role of pulmonary vasodilator therapy in LV dysfunction with disproportionate PH (ie, LEPHT—Left ventricular systolic dysfunction associated with Pulmonary Hypertension Riocigat Trial).⁷³ Further defining the extent of disproportionate PH (ie, ΔPVR) vs LV dysfunction (ie, ΔPCWP) during exercise may offer improved patient phenotyping to inform targeted interventions.

Chronic Obstructive Pulmonary Disease

Pulmonary hypertension is a well-known complication of chronic obstructive pulmonary disease (COPD). Descriptions of mPAP response patterns to exercise in COPD are limited by the heterogeneity in the small cohorts studied. In Hickam's original series, despite normal average resting mPAP (18 ± 4 mm Hg), the average increment in mPAP relative to CO was steeper in patients with emphysema (4.0 ± 1.7) relative to normals (0.9 ± 1.4). Blanco et al found an even steeper increment in mPAP relative to CO (7.0 mm Hg/L) in patients with COPD selected on the basis of resting mPAP >20 mm Hg.⁷⁴

In a third study of 10 subjects undergoing lung volume reduction surgery with mild PH (resting mPAP = 26 ± 6 mm Hg), mPAP at rest and during exercise were examined relative to the degree of thickening of excised small ($100\text{--}200$ μm diameter) muscular pulmonary arteries (ie, intima + media as a percentage of vessel diameter) as an indicator of pulmonary arterial remodeling. Interestingly, there was no relationship between resting mPAP and arterial wall thickness, but exercise PAP and change in PAP with standardized exercise (25W) were strongly related to wall thickness ($R=0.72$ and $R=0.90$, respectively, both $P<0.05$). The authors acknowledge the multiple potential mechanisms mediating PH in emphysema beyond vascular remodeling. However, based on these findings exercise PH may be indicative of reduced recruitability and distensibility of pulmonary vessels and the degree of the remodeling cannot be estimated by resting mPAP.

Mitral Valve Disease

The development of PH in the presence of mitral stenosis (MS) and mitral regurgitation (MR) has been well described for over 40 years,^{75,76} yet mechanisms mediating heterogeneity in pulmonary vascular responses to left atrial hypertension among patients with mitral valve disease at rest and during exercise remain incompletely understood.^{77,78} Schwammenthal et al showed that elevated PAP at rest and during exercise in MS is closely related to net atrioventricular compliance, to a

greater extent than mitral valve area.⁷⁹ Reduced compliance (<4 ml/mm Hg) predicted the need for mitral valve replacement (MVR) or commissurotomy and defines an MS cohort in which PH is closely linked to functional capacity.⁸⁰

PHARMACOTHERAPIES FOR TREATMENT OF PAH ALTER EXERCISE PAP

The observed improvements in exercise capacity with short-term aerosolized iloprost exposure, despite minimal changes in resting hemodynamics,⁸¹ led Blumberg and colleagues to hypothesize that iloprost would elicit more favorable effects on pulmonary hemodynamics during exercise than at rest. Indeed, one-time dose of iloprost was associated with a $6 \pm 8\%$ reduction in resting PAP and an $18 \pm 11\%$ fall in exercise PAP at a standardized submaximum workload (25W or 50W, $P<0.05$) in a cohort consisting of primarily Group 1 PH.⁶⁰ One limitation of this study was the short duration between exercise studies that raised the possibility of reduced PAP responses on the post-intervention study on account of repeated testing. A second small study ($n=5$) of PAH patients with implantable hemodynamic monitors (ChronicleR IHM, Model 9520, Medtronic, Minneapolis, MN) also showed reduction in PAP with iloprost during submaximal exercise.⁶¹

Calcium channel antagonists have been shown to reduce absolute values of exercise mPAP and PVR and to blunt the increment in mPAP during exercise in PAH⁸² and PH due to COPD^{83,84} despite patients achieving a greater workload. In contrast, hydralazine did not reduce exercise PAP in a similar, small study, but did reduce PVR because CO increased.⁸⁵ This study is an example of why mPAP alone is insufficient, as greater CO with hydralazine resulted in equal mPAP at peak exercise but lower PVR. Further work is needed to ascertain whether there are treatment-specific approaches that differentially modulate pulmonary hemodynamics during exercise.

The influence of PDE5 inhibitors on exercise pulmonary hemodynamics has been studied in secondary forms of PH. Our group demonstrated that sildenafil, administered over 12 weeks in a random-

ized, double-blind, placebo-controlled trial (average dose of 50 mg every 8 hours), led to improved peak VO_2 and a reduction in exercise PVR.⁶⁵ The magnitude of reduction in exercise PVR in this study was strongly related to the degree of improvement in peak VO_2 . Subsequent studies have found similar improvements in exercise capacity in HFrEF.

However, large-scale outcomes trials of other pulmonary vasodilators for the treatment of HF have been disappointing to date.^{86,87} These studies did not stratify HF subjects by rest and/or exercise pulmonary hemodynamics to focus on subjects with disproportionate elevations in PVR relative to PCWP.

FUTURE DIRECTIONS

RV-Pulmonary Vascular Interactions

Characterization of pulmonary vascular response patterns to exercise to date have largely focused on changes in PAP and PVR, which is simply a measure of opposition to the mean component of flow. However, the pulmonary vasculature is a low resistance, high compliance system, making the pulsatile component of hydraulic load and wave reflection important to consider as well.⁸⁸ Impedance is the measure of opposition to pulsatile components of flow and provides a more complete indicator of RV afterload.⁸⁹ Several studies have described changes in resting impedance arising from large-artery stiffening and remodeling in PH.⁹⁰ This abnormal pulsatile load may have detrimental effects on ventricular-vascular coupling, unfavorably loading the still-ejecting RV. Measurements of impedance in the frequency domain, and pressure-wave forms in the time-domain during exercise are needed to more completely characterize RV-pulmonary artery interactions during exercise. Whether RV responses to increased pulsatile flow during exercise predict future development of RV dysfunction or response to specific PH therapies merits further investigation as well.

Further development and validation of multimodality noninvasive methods to characterize RV-pulmonary artery structure and function during exercise hold promise in advancing our understanding of pulmonary vascular responses to exer-

cise. Finally, future studies are needed to define the natural history of “early” forms of PH unmasked by exercise (ie, EIPAH and HFpEF) and the extent to which these conditions may be amenable to treatment.

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