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Pulmonary Vascular Disease: Hemodynamic Assessment and Treatment Selection—Focus on Group II Pulmonary Hypertension

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Abstract

Purpose of Review Pulmonary hypertension due to left heart disease (PH-LHD) is the most common cause of pulmonary hypertension worldwide, yet therapies used to treat pulmonary arterial hypertension have failed to show efficacy in this population. Proper hemodynamic assessment and differentiation of pulmonary hypertension phenotypes is therefore critical for both current clinical practice and future research and therapeutic efforts.

Recent Findings Substantial recent efforts have sought to improve the hemodynamic characterization of pulmonary hypertension for both diagnostic and prognostic purposes. These efforts include identifying occult LHD using provocative maneuvers as well as sub-classifying PH-LHD based on the presence or absence of a pre-capillary component. How to best define the pre-capillary component remains controversial as several studies have drawn conflicting conclusions. The lack of standardization of hemodynamic measurements as well as measurement fidelity concerns may explain some of the discrepant results. Non-hemodynamic methods of PH-LHD classification may also have an emerging role. Despite recent advances, therapeutic studies have largely remained disappointing.

Summary In this review, we discuss the nuances and controversies surrounding diagnostic and prognostic hemodynamic characterization of PH-LHD as well as summarize the recent therapeutic efforts and ongoing challenges in this population.

Keywords Pulmonary hypertension · Left heart disease · Right heart catheterization · Hemodynamics

Introduction

Pulmonary hypertension (PH) associated with left heart disease (PH-LHD) is the most common form of PH worldwide and is associated with a worse prognosis than LHD without PH. Further, the presence of a pre-capillary component portends an even worse prognosis [1–3]. Despite its increasing recognition, there is lack of well-defined therapeutic options, and its hemodynamic assessment provides unique challenges. Here we review contemporary literature describing the recent advances in this field and the complexities in the hemodynamic assessment and management of PH-LHD.

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Hemodynamic Definition and Classification of PH-LHD

PH-LHD is defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, in the presence of elevated pulmonary arterial wedge pressure (PAWP) or left ventricular end diastolic pressure (LVEDP) > 15 mmHg [2, 4]. An increase in left-sided filling pressures differentiates this from World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH). PH-LHD can be associated with heart failure with reduced ejection fraction (HFrEF), HF with preserved EF (HFpEF), left-sided valvular disease, or congenital cardiomyopathies [5].

An increase in PAWP initially causes a passive increase in pulmonary pressure or "isolated post-capillary PH (IpcPH)", where the pulmonary pressures typically normalize with a reduction in PAWP. The diastolic pulmonary gradient (DPG = diastolic pulmonary artery pressure [dPAP] − PAWP), the transpulmonary gradient (TPG = mPAP − PAWP), and the pulmonary vascular resistance (PVR = TPG/cardiac output [CO]) are not significantly

elevated (DPG < 7 mmHg, TPG < 12–15 mmHg and PVR < 3 Woods Unit [WU]) [2].

The prevailing paradigm is that persistent elevation in PAWP and ongoing heart failure provokes alveolar wall injury, pulmonary vasoconstriction, and sometimes, remodeling of the small resistance pulmonary arteries (PA) [6]. This leads to development of a pre-capillary component where pulmonary pressures increase out of proportion to PAWP. This has been coined "combined post- and pre-capillary PH (CpcPH)" and is characterized by an elevated DPG, TPG, and PVR. Interventions directed towards acute reduction in PAWP may not necessarily normalize pulmonary pressures [2], and CpcPH is associated with worse prognosis than IpcPH as well as LHD without PH [3]. Recent studies investigating hemodynamic classification and outcomes in PH-LHD are summarized in Table 1.

Diastolic Pulmonary Gradient and Updated Classification of PH-LHD

At the 5th World Symposium on PH in Nice, France, it was proposed that DPG should be the sole discriminator of IpcPH (DPG < 7 mmHg) and CpcPH (DPG ≥ 7 mmHg) [1]. This proposal was based on sound physiologic rationale: elevated left heart filling pressures lower pulmonary arterial compliance (PAC) independent of resistive load, increasing the pulmonary pulse pressure. As pulse pressure increases, mPAP increases out of proportion to dPAP, thereby indirectly raising the TPG and PVR [18]. The DPG is assessed during cardiac diastasis, eliminating contributions of flow state and the arterial Windkessel model. The dPAP is approximately equal to the PAWP and DPG is < 5 mmHg in most patients with LHD [8, 19].

Gerges et al. have demonstrated a worse prognosis in patients with PH-LHD and an elevated DPG ≥ 7 mmHg, both in the setting of an elevated TPG (≥ 12 mmHg) and when DPG is considered in isolation [7•, 20]. However, many other studies have failed to reproduce the prognostic value of DPG in both HFrEF and HFpEF [8, 9•, 10, 13, 21]. There are several factors that likely contribute to the discrepant results. First, as heart rate increases and diastole shortens, the gradient between dPAP and PAWP increases, irrespective of presence or absence of pre-capillary disease. Thus, significant tachycardia can raise the DPG [22]. Second, right ventricular (RV) function and adaptation to its afterload may have a more significant impact on prognosis than pulmonary vascular pressures (or disease) alone [23, 24]. Incorporation of flow (via stroke volume—a marker of ventricular function) may explain why PVR has proven to be a more robust prognostic marker than DPG or TPG. The fact that prognosis is also poorer in the setting of very low or negative DPG [9•] may suggest that LHD drives outcomes independent of pulmonary vascular disease. These data also remind us that the lack of a clear

prognostic signal does not necessarily preclude the use of DPG as a diagnostic variable. Finally, the observation of frequent negative DPG values illustrates the challenges in accurately measuring the DPG [8, 9•, 12]. Lack of measurement standardization and artifact associated with use of fluid filled catheters undoubtedly contribute and will be discussed in sections below.

Recognizing some of the limitations of DPG, in 2015, European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines redefined CpcPH as mPAP ≥ 25 mmHg, mean PAWP > 15 mmHg, DPG ≥ 7 mmHg, and/or PVR > 3 Wood units. [4] There are ongoing concerns that the "or" portion of this definition can significantly raise the number of patients with CpcPH, based on an increase in PVR alone [25]. Additionally, Palazzini and colleagues did not find the new ERS/ERS definition predictive of worse outcome in their cohort [13•]. Most recently, Guazzi and Naeije have proposed defining CpcPH as DPG ≥ 7 mmHg and PVR > 3 Wood units, reasoning that an elevated DPG in the setting of a normal PVR is likely a false positive [23]. Whether this provides superior prognostication remains to be studied.

Despite the complexities in defining CpcPH, the data in totality show us that CpcPH has a worse prognosis as compared to Ipc-PH [13•] with a distinct pathophysiology. In an exploratory analysis of CpcPH patients, Assad et al. found genes and biological pathways in the lung known to contribute to PAH pathophysiology [11•]. Exercise breathing patterns in CpcPH are also more similar to PAH than IpcPH with a reduced prevalence of exercise oscillatory breathing [17]. Because of the outlined limitations of a purely hemodynamic definition, there is an ongoing need to develop biomarker or non-hemodynamic strategies to more precisely phenotype and accurately define CpcPH.

Pulmonary Arterial Compliance

PVR only describes the load imposed on the RV during steady-state blood flow. Pulmonary arterial compliance (PAC) is a second determinant of afterload that accounts for the pulsatile nature of blood flow. PAC specifically quantifies the distensibility of the pulmonary vasculature relative to changes in volume. PAC can be estimated a number of ways, most simply as stroke volume [SV]/PA pulse pressure. In the normal lung, PVR and PAC are inversely related and their product (RC time) is nearly constant. Thus, an increase in PVR is accompanied by a proportional decrease in PAC, over a wide range of severities of PH [26]. However, in LHD, an increase in PAWP further lowers PAC for any given PVR, thereby increasing RV pulsatile afterload [18]. Thus, in the unique setting of LHD, PAC bundles the effect of two hemodynamic measurements (PAWP and PVR), and is a more complete marker of total RV afterload. Not surprisingly, PAC is a

Table 1   Recent studies investigating hemodynamic classification and outcomes in PH-LHD

Diagnostic/prognostic studies

Study	Major findings
Vachiery et al. J Am Coll Cardiol, 2013. 62(25 Suppl): p. D100-8 [1]	• 5th World symposium on PH • Proposed new classification schema for PH-LHD
Gerges et al. Chest, 2013. **143**(3): p. 758–766 [7•]	• Found that in patients with post-capillary PH and TPG > 12 mmHg, DPG ≥ 7 mmHg was associated with a worse median survival • In 18 patients, lung tissue in patients with elevated DPG was evaluated and showed advanced remodeling of the vasculature.
Tedford et al. J Heart Lung Transplant, 2014. 33(3): p. 289–97 [8]	• DPG did not predict post-transplant survival after heart transplant in a patient population with pre-transplant PH (UNOS database).
Tampakakis et al. JACC Heart Fail, 2015. 3(1): p. 9–16 [9•]	• In a retrospective, largely HFrEF cohort, DPG was not associated with mortality in PH-LHD. TPG and PVR both predicted mortality. • 36% of PH-LHD patients had a negative DPG.
Al-Naamani et al. JACC Heart Fail. 2015 Jun;3(6):467–474 [10•]	• Pulmonary vascular compliance was the best predictor of mortality in a PH-HFpEF cohort. DPG did not predict outcome. • Acute vasodilator response was not associated with improved survival (inhaled NO).
Galie et al. Eur Heart J, 2016. **37**(1): p. 67–119. [4]	• ESC/ERS guidelines for PH. • Most recent classification of PH, pre-capillary PH, post-capillary PH, isolated post-capillary PH, and combined post- and pre-capillary PH
Assad TR J Am Coll Cardiol. 2016 Dec 13;68(23):2525–2536 [11•]	• Patients with Cpc-PH had genetic polymorphisms shared with PAH that were not present in Ipc-PH patients.
Nagy et al. Eur J Heart Fail. 2017 Jan;19(1):88–97. [12]	• Negative DPG was associated with large PAWP V-waves and carried a better prognosis than a positive DPG.
Palazzini M et al. Eur J Heart Fail. 2017 May 2. https://doi.org/10.1002/ejhf.860. [Epub ahead of print]. [13•]	• In PH-LHD patients, using the revised ESC/ERS guidelines, no difference in survival was noted between Cpc-PH and Ipc-PH. • PVR had a better predictive value than DPG in PH-LHD patients.
Adir et al. Am Heart J. 2017 Oct;192:120–127. [14]	• DPG was higher in PH-HFpEF than in PH-HFrEF patients • Pulmonary vascular compliance predicted survival; DPG did not.
Wright et al. Circ Heart Fail. 2017 Sep;10(9). [15•]	• Employing QRS-gated methods to assess the PAWP led to overall higher DPG values, a greater proportion of Cpc-PH patients, and fewer negative DPG values compared to usual methods.
Ghio et al. Eur J Heart Fail. 2017 Nov 16. doi: 10.1002/ejhf.1067 [16]	• During vasodilator challenge, Cpc-PH patients demonstrate more improvement in PVR, TPG, and DPG compared to Ipc-PH patients.
Caravita et al. J Heart Lung Transplant. 2017 Jul;36(7):754–762 [17]	• Patients with Cpc-PH had similar exercise-induced ventilatory patterns (less oscillatory breathing, more hyperventilation) to PAH patients when compared to Ipc-PH patients.

superior prognostic marker to both PVR and DPG in predicting RV failure and adverse outcomes in PH-LHD [10•, 14, 27, 28]. It however is not helpful in differentiating IpcPH and CpcPH.

Hemodynamic Assessment of PH-LHD

Right heart catheterization (RHC) is the gold standard for diagnosis of PH. It is safe even in the setting of severe PH and is associated with low morbidity at experienced centers [4]. A RHC should always be performed before any PH-specific therapy is initiated. Preferred access sites include right internal jugular vein or antecubital vein, with the femoral vein as an alternative. Local anesthesia is used to facilitate line placement. Systemic sedation should generally be avoided, with preference for oral sedative medications, if needed. The patient remains supine with legs flat during the study. Blood pressure (BP) and systemic arterial oxygen saturation should be monitored. Care must be taken to properly flush pressure lines and ensure equipment calibration is up to date. The pressure transducer should be zeroed at the level of the left atrium which corresponds to the mid-thoracic line (halfway between the anterior aspect of the sternum and the table surface) [1, 29]. Pressures should always be accompanied by a simultaneous ECG recording and are recorded in the right atrium (RA), right ventricle (RV), pulmonary artery (PA), and the wedge positions while the patient is breathing spontaneously. Breath hold maneuvers are not recommended [30, 31]. Waveforms are analyzed at end-expiration when intra-

thoracic pressures have the least effect on resting pressure measurements. A PAWP saturation (blood sample taken from the distal port while in the wedge position) should always be checked to ensure an adequate wedge, particularly when the PAWP is elevated. The PAWP saturation should be within 5% of the systemic oxygen saturation. An LVEDP should be measured when PAWP cannot be measured or the measured PAWP seems inconsistent with the clinical picture.

If tracings appear dampened (e.g., loss of a dicrotic notch in the PAP tracing or blunted RV end-diastolic pressure inflection point), catheter and tubing should be flushed to remove any air. Catheter whip may occur in high CO states and is minimized by relocating the catheter to a less turbulent area. More common than catheter whip, catheter ringing occurs as the heart rate approaches the inherent resonant frequency of the fluid filled catheter system. Microbubbles in the fluid-filled catheter exacerbate this issue by increasing the compliance of the system [32]. After thoroughly flushing the system, if catheter ringing is still present, a filter can be introduced [33] or more commonly a small amount of denser fluid (blood or contrast) can be added to the catheter [34]. However, the latter strategy can result in over-dampening of the waveform, with a resultant decrease in the sPAP and increase in the dPAP (Fig. 1a, b). This further illustrates the inherent limitation of using DPG as a diagnostic or prognostic marker in PH-LHD.

Measurement of PAWP—Important Considerations and Caveats

The PAWP should be measured at end-diastole to reflect the LVEDP and confirmed with a wedge saturation, especially when the PAWP is elevated. Several publications have highlighted the lack of standardization of the PAWP measurement and the potential impact on pre-capillary parameters,

especially the DPG [12, 15•, 35–38]. Use of the "mean"-PAWP value, which is averaged over the entire cardiac cycle and incorporates the V wave, results in lower or even negative DPG values when compared to measuring PAWP at end-diastole (typically as mean of the "a" wave or pre c-wave) and can significantly vary from measured LVEDP, leading to misclassification of PH [39]. This is particularly relevant in the presence of atrial fibrillation [35] and prominent V waves [12], where end-diastolic PAWP correlates best with LVEDP [40]. Wright and Mak recently proposed a novel approach to estimate PAWP near end-diastole with EKG gating [15•]. At least for the purposes of assessing for a pre-capillary component of PH where high accuracy and reproducibility in dPAP and PAWP is required, estimating PAWP at end-diastole appears to be the most appropriate technique. Perhaps just as relevant, they also described the impact of a fluid-filled catheter artifact on the dPAP [15•]. Whether more standardized approaches to measure the PAWP or the use of high-fidelity catheters to minimize artifact would improve the prognostic value of the DPG requires further study.

Estimation of Cardiac Output

The gold standard for estimating CO is the direct Fick method that involves measuring VO2 or oxygen consumption [CO = VO2 / systemic arteriovenous oxygen difference] [41]. As the required equipment for measuring oxygen consumption is cumbersome and not widely available, thermodilution (TD) [42] and the estimated Fick method are commonly used. TDCO should be measured in triplicate at end-expiration [4, 43]. Although the validity of TDCO has been questioned in the setting of low or high CO or severe tricuspid regurgitation [44–46], other studies have reported an agreement between TD and direct Fick, validating its use even under those
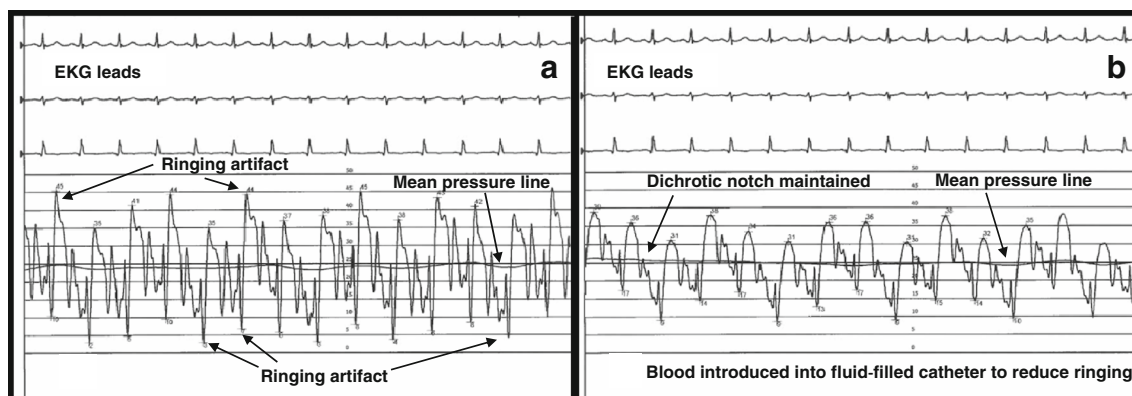

Fig. 1 Pulmonary artery (PA) tracings from the same patient during a single right heart catheterization procedure. **a** A high degree of "ringing" artifact when using a fluid-filled catheter. Note the difficulty this poses in determining both the systolic and diastolic PA pressures. **b** PA tracing after a small amount of blood was aspirated into the catheter to change the compliance of the catheter. Note the reduced ringing artifact.

However, now the systolic pressure is lower, and the diastolic pressure is higher. It is possible to over-dampen the tracing by this method, and a false elevation in the diastolic pressure may lead to a falsely elevated diastolic pulmonary gradient, misclassifying a patient as Cpc-PH. Note that the mean PA pressure is nearly the same in both tracings

circumstances [41, 47]. TDCO may be inaccurate in the presence of intra-cardiac shunts and should not be used in this circumstance. The estimated Fick method relies on estimating VO2 and is prone to error in heart failure, PH, or abnormal body habitus [48–50]. Discrepancies between different methods have a wide range of implications for the diagnosis and management of PH-LHD [51]. In an analysis of more than 15,000 adults undergoing RHC, TDCO and estimated Fick methods correlated poorly, varying by > 20% in a third of the patients. TDCO estimates were superior to estimated Fick in predicting all-cause mortality [52]. In the absence of an intra-cardiac shunt, TD is the recommended method to assess CO [30, 31].

Vasodilator Testing

Vasodilator testing is recommended during RHC in heart transplant candidates with CpcPH as absence of reversibility precludes eligibility for heart transplantation (HT) [53, 54]. The risk of early death presumably from RV failure is elevated when PVR > 5 WU or TPG > 15 mmHg [55, 56], and the risk increases incrementally with increasing PVR [57]. In a classic study of 293 patients undergoing evaluation for HT with vasodilator testing using intravenous (IV) nitroprusside [53], mortality was highest in patients whose PVR failed to drop below 2.5WU, followed by patients in whom the PVR was ≤ 2.5 WU, but nitroprusside administration resulted also in systemic hypotension (systolic BP (SBP) to < 85 mmHg). Short-term survival was similar in patients with an appropriate decrease in PVR without systemic hypotension compared with patients with normal PVR at baseline. Several subsequent studies have used various other vasodilators (nitroglycerin), inotropes (dobutamine, milrinone), inhaled nitric oxide (iNO), prostaglandin E1, inhaled or intravenous prostacyclin, and sildenafil for the evaluation of the reversibility of PH with varying effects on hemodynamics [58–62]. A contemporary meta-analysis revealed that sodium nitroprusside resulted in the most profound lowering of PAWP, while PAWP increased with iNO [63]. Nitroprusside and milrinone led to a most significant increase in cardiac output while prostacyclin and prostaglandin E1 exerted the most reduction in PVR.

The International Society for Heart and Lung Transplantation (ISHLT) recommends PVR > 5 WU or TPG > 15 mmHg as a relative contraindication to HT, although many centers consider extending this to a PVR > 3WU [54]. If PVR can be reduced to ≤ 2.5 WU without systemic hypotension, patients can be accepted as candidates. The guidelines do not provide recommendations on which vasodilator to use, and the choice is often determined by the center's practice.

In general, for HT candidates with PVR > 3–5 WU and TPG > 15 mmHg, with elevated PAWP and systemic vascular resistance (SVR), and SBP > 90 mmHg, IV nitroprusside is our initial vasodilator of choice (prostaglandin E1 is an acceptable alternative). Elevation in PAWP alone can raise the PVR by multiple mechanisms [18, 64–66]. If PVR remains high despite lowering PAWP, we would consider addition of iNO or inhaled prostacyclin. In the absence of significantly elevated PAWP, and especially if CO is very low and mPAP is modestly elevated, we would consider the use of IV milrinone [58] with possible addition of iNO. In the absence of a reduced CO and normal or near normal PAWP, we consider the use of more selective pulmonary vasodilators including IV or inhaled prostacyclin, with preference for inhaled prostacyclin or iNO if SBP is low.

When an acute vasodilator challenge is unsuccessful, prolonged administration of vasodilators over 24 to 48 h maybe necessary. Some patients require longer duration of vasodilator therapy over days to weeks with serial RHC [67], and if still unsuccessful, are classified as irreversible PH-LHD, needing consideration for mechanical circulatory support (MCS) [2]. Most patients with "irreversible" PH-LHD still normalize PVR after MCS support, suggesting that a persistent "functional" component of PH exists in these patients [68–70] rather than significant pulmonary vascular remodeling.

In a retrospective analysis of the United Network of Organ Sharing (UNOS) data, an elevated DPG (using multiple cutoffs), even in combination with elevated PVR or TPG, failed to predict post-transplant mortality [8]. Using the updated classification of PH-LHD, Ghio et al. recently found that CpcPH patients had more significant improvement in PVR, TPG, and DPG during vasoreactive testing as compared to IpcPH patients [16]. Thus, the new classification of CpcPH does not help to identify irreversible PH-LHD. Al-Naamani and colleagues also found that vasoreactivity did not predict prognosis in their cohort of HFpEF patients with CpcPH [10•]. Currently, outside of assessing transplant candidacy, there is no clinical role for vasodilator testing in PH-LHD.

Provocative Testing

In the context of LHD, provocative testing during RHC with fluid challenge or exercise is helpful for evaluating exertional dyspnea of unknown origin with normal resting hemodynamics, in identifying early stages of LHD [71], and differentiating HFpEF from PAH in patients with normal PAWP at rest (Table 2) [77]. PAWP of course may be reduced to < 15 mmHg with diuresis or afterload reduction prior to RHC, leading to misclassification of PH [9•]. Provocative testing may also be helpful in identifying exercise induced PH (EIPH) [78, 79], preload insufficiency [80], and defining RV contractile reserve [81], though these latter topics are beyond the scope of the current review.

Table 2 Provocative studies and major findings

Provocative studies	
Study	Major findings
D'Alto et al. Chest, 2017. **151**(1): p. 119–126 [72•]	• Using a cutoff of 18 mmHg for the PAWP, fluid challenge with 7 mL/kg of saline allowed reclassification of 6–8% of patients from precapillary PH or normal to PH-LHD
Robbins et al. Circ Heart Fail, 2014. 7(1): p. 116–22. [73]	• After 500 cm^3 normal saline fluid challenge, > 22% of patients originally classified as PAH were reclassified as post-capillary PH using a cutoff of PAWP of > 15 mmHg
Hsu et al. Pulm Circ. 2017 Mar; 7(1): 253–255. [74•]	• Compared with direct Fick, thermodilution underestimated cardiac output during exercise.
Wright et al. Heart, 2016. 102(6): p. 438–43 [75•]	• Described the pulmonary pressure response to sustained, submaximal exercise in healthy volunteers. Found that PAWP may routinely increase to > 20 mmHg early in exercise, and that PAWP and PA pressures may decline during continued exercise
Wolsk E et al. JACC Heart Fail, 2017. 5(5): p. 337–346 [76]	• Despite similar baseline hemodynamics in healthy controls, there was a marked difference in exercise response in patients based on age. Older patients had increased filling pressures and diminished cardiac output with leg raise. 30% of older patients reached a PAWP of ≥ 25 mmHg.
Kovacs G. Eur Respir J. 2017 Nov 22;50(5) [31]	• Position statement on invasive exercise hemodynamic testing

Fluid Challenge

It is important to remember that PAWP increases in healthy patients in response to a fluid bolus. However, patients with HFpEF exhibited a steeper increase in PAWP relative to the infused volume, as compared to healthy controls [82]. The volume and rate of fluid administration have clinical relevance, as slower infusions can lead to re-distribution into intra-vascular spaces [83], while more rapid infusions maybe poorly tolerated in HF [73, 82, 84]. In a retrospective analysis of 287 patients, including 202 patients labeled as non-group 2 PH, with mPAP ≥ 25 mmHg and PAWP ≤ 15 mmHg at rest, a fluid challenge of 500 cm^3 of normal saline over 5–10 min led to a re-classification of 22% of patients as having occult pulmonary venous hypertension, based on an increase in PAWP to > 15 mmHg [73]. These patients had clinical, echocardiographic, and hemodynamic characteristics comparable to HFpEF patients, suggesting a distinct phenotype from PAH. However, a PAWP > 15 mmHg with fluid bolus can be seen in normal controls where a PAWP > 18 mmHg was not witnessed in healthy controls [63].

More recently, D'alto et al. studied 212 patients referred for RHC for evaluation of PH who underwent hemodynamic measurements before and after the administration of 7 ml/kg of saline over 5–10 min (~ 500 cm^3) [72•]. After fluid administration, 8 and 6% of patients initially classified as no-PH and pre-capillary PH, respectively, were re-classified as post-capillary PH based on an increase in PAWP > 18 mmHg. Similar to prior studies [82], patients with PH-LHD had a steeper increase in PAWP, while the PAWP in patients without PH did not increase to > 18 mmHg. Interestingly, the DPG decreased with fluid challenge, as an acute rise in PAWP can be accompanied by a slower rise in dPAP due to the preserved distension of the resistive PAs [85].

The effect of pericardial constraint on ventricular interaction can also increase PAWP in response to a fluid challenge, in patients with normal hemodynamics [82] as well as RV pressure overload [83, 86]. RAP approximates pericardial pressure, and thus an increase in LV transmural pressure (PAWP − RAP) is suggestive of LHD as opposed to pericardial constraint. In the study by D'Alto et al., this increased only in patients with either overt or occult PH-LHD [72•].

In summary, an increase in PAWP > 18 mmHg in response to a fluid challenge with 500 cm^3 of saline administered over 5–10 min may be useful to identify occult PH-LHD, particularly if accompanied increasing LV transmural pressure. Although exercise may be a more sensitive provocative test than fluid challenge to identify PH-LHD [84], the potential advantages of a fluid challenge include less variation with HR and blood pressure, less catheter artifact and dependence on patient's exercise capacity, and the widespread availability of necessary equipment compared to what is required for exercise.

Exercise RHC

Exercise induces elevation in CO, PAWP, and/or PAP in normal subjects with increasing age [87], and those with HF or PH [71, 88, 89]. It is typical to perform an exercise RHC under a ramp protocol of incremental workloads (2–3 min per stage) with measurement of RAP, PAWP, mPAP, and CO at each stage [31]. Accurate leveling of the transducer is mandatory, and may be particularly challenging for upright exercise [31]. Bicycle exercise is preferred to upper extremity exercise, to avoid increased systemic vascular resistance with the latter. Fluid-filled catheters often result in excessive ringing and motion artifacts during exercise; therefore, only mean pressures should be

measured. Large intra-thoracic pressure changes can occur during exercise leading to over-estimation of pressures if measured at end-expiration, especially in lung disease [90, 91]. Therefore, averaging the measurements over the respiratory cycle is recommended. Lastly, care must be taken to ensure an adequate PAWP. A recent position statement on exercise hemodynamics details many of these issues [31].

Exercise-Induced Changes in PAWP

An increase in PAWP of 10 mmHg or more may be observed with exercise in healthy controls [84, 89, 92, 93], with an average of 5 mmHg greater rise with supine vs upright exercise, although the absolute change in PAWP is similar [93]. However, there are several factors that affect this response. Exercise-induced increase in PAWP is more marked in older patients [76]. Changes in PAWP also vary with the duration and intensity of exercise. PAWP may exceed 20 mmHg early in exercise, but decline significantly within minutes [75•]. Such brief and early increases in PAWP may not be pathologic, and thus, measurements at multiple time points may be helpful. Exercise can also induce a ~ 2-fold greater increase in PAWP as compared to fluid challenge in patients with HFpEF, although exercise pressures were measured at end-expiration in this study [84]. In general, we consider an abnormal PAWP to be ≥ 25 mmHg with supine exercise or ≥ 20 mmHg with upright exercise, averaged over the entire respiratory cycle. In those over the age of 60, PAWP ≥ 25 has been reported in up to 30% of subjects apparently free of cardiovascular disease. Thus, exercise PAWP should be considered in the context of age [76], and age-specific definitions have also been proposed [94]. The effect of significant pericardial constraint should be excluded by considering the transmural LV pressure [83].

Exercise-Induced Changes in Cardiac Output

CO during exercise is best measured with the direct Fick method [31]. Oxygen saturations, hemoglobin concentration, and oxygen consumption should be measured. TDCO is considered an alternative if equipment for direct Fick is unavailable. However, the TD method can underestimate the CO as compared to the direct Fick method, particularly at higher outputs [74•].

Treatment Selection in PH-LHD

The primary treatment of PH-LHD is the management of the underlying LHD. There are no PAH-specific therapies currently approved for PH-LHD; rather, interventions are directed towards relieving symptoms of dyspnea and improving exercise capacity, or defining eligibility for HT [1, 2].

Treatment of PH-HFrEF

The cornerstone of treatment of PH-HFrEF is the use of guideline-directed therapies including beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACE-I), or angiotensin receptor blockers (ARBs) or angiotensin receptor-neprilysin inhibitor (ARNI), aldosterone-antagonists, and hydralazine/nitrate combination [95, 96]. Relief of congestion with diuretics and vasodilators can improve PAPs and may require invasive monitoring [95, 97, 98]. Reducing left heart filling pressures alone may significantly lower PVR as discussed above. Non-pharmacologic therapies include consideration for cardiac resynchronization therapy when appropriate and MCS for suitable candidates [95]. Reversibility of fixed PH can occur with MCS, allowing candidacy for HT [99, 100].

PAH-specific therapies have been trialed in PH-LHD on the basis of PH being driven by increased endothelin-1 activity [101, 102] and impaired NO-dependent vasodilation [103]. However, studies involving parenteral prostacyclins [104] and endothelin receptor antagonists (ERA) [105–108] in HFrEF have demonstrated negative or neutral effects, and even trends towards harm [109, 110].

Sildenafil, a phosphodiesterase-5-inhibitor (PDE-5-I), promotes NO-dependent vasodilation by preventing the degradation of cyclic guanosine monophosphate (cGMP) [111]. In single-center studies, sildenafil has been shown to decrease TPG, increase CO [112], and improve exercise hemodynamics, VO2 [113], exercise capacity, and quality of life in HFrEF [114]. However, these studies used higher doses of sildenafil (25 to 75 mg three times daily [TID]) than what is approved for PAH therapy. A multicenter trial (SilHF, NCT01616381) to evaluate a lower dose of sildenafil in PH-HFrEF is currently ongoing. A retrospective study has suggested that sildenafil lowers mPAP and PVR in those with persistent PH after MCS implantation [115]. A randomized, placebo-controlled, multi-center study (SOPRANO, NCT02554903) is currently investigating the use of the ERA Macitentan in this clinical scenario.

Riociguat, a soluble guanylate cyclase (sGC) stimulator, sensitizes sGC to endogenous NO and directly stimulates sGC independent of NO, inducing vasodilation [116]. In the LEPHT trial, multiple doses of riociguat (0.5, 1, and 2 mg TID) were compared to placebo in 201 patients with PH-HFrEF. The study failed to meet the primary end point of reduction in mPAP after 16 weeks, but improved cardiac index and PVR [117]. Similarly, in SOCRATES-REDUCED, vericiguat did not meet the primary end point of reduction in NT-proBNP [118] compared with placebo in 456 patients with HFrEF (PH was not a requirement for study entry).

Treatment of PH-HFpEF

The management of HFpEF is limited to diuretics for the relief of volume overload and treatment of underlying conditions including hypertension, coronary artery disease, atrial fibrillation, and sleep apnea [95]. It is reasonable to control BPs with BB, ACE-I, or ARBs, although none of these drugs conclusively improve outcomes in HFpEF [95]. Aldosterone antagonists are recommended to reduce HF hospitalizations in eligible HFpEF patients [96, 119]. Nitrate therapy is ineffective in HFpEF to improve exercise tolerance or quality of life [120].

PAH-specific therapies have been studied in HFpEF with limited benefit. Sildenafil 50 mg TID improved hemodynamics and echocardiographic measures of RV function, in a placebo-controlled, single-centered trial of 44 patients with CpcPH in HFpEF at 6 months, with continued benefit at 1 year [121]. However, in a subsequent single-center study and in the RELAX study, sildenafil did not improve mean PAP, PAWP, CO, [122] exercise tolerance, or VO2 in HFpEF [122, 123]. Post hoc analysis from the RELAX study revealed that sildenafil failed to result in any significant reduction in RV afterload and likely reduced LV contractility [124]. The DILATE-1 trial compared multiple doses of riociguat (0.5, 1, and 2 mg) to placebo in 39 patients with PH-HFpEF including five with CpcPH. There was no significant change in mPAP at 6 h (primary end point) or PVR. Riociguat 2 mg as compared to placebo increased SV, lowered SVR, and decreased RV end-diastolic area, without increasing PAWP [125]. In another phase 2 study SOCRATES-PRESERVED, vericiguat did not change the primary end points of NT-proBNP and left atrial volume at 12 weeks compared with placebo in 477 patients with HFpEF (presence of PH was not an inclusion criteria), although there were some improvements in quality of life metrics [126].

Recent trials of ERAs in HFpEF have been largely disappointing. A selective endothelin A receptor antagonist, sitaxsentan, improved treadmill exercise time compared with placebo in 192 patients with HFpEF after 6 months of therapy, without an improvement in LV mass or diastolic indices [127]. The BADDHY Trial evaluated 12 weeks of therapy with bosentan vs placebo in 20 patients with PH-HFpEF, including 4 with CpcPH, demonstrated worsening PAP and RAP with bosentan [128]. The MELODY Trial evaluating macitentan in 63 patients with CpcPH, LVEF > 30%, most of whom had HFpEF, demonstrated no significant difference in the primary end point of worsening functional class or fluid retention, although more patients receiving macitentan had worsening fluid retention, without significant reduction in RAP or PVR after 12 weeks of treatment [129] compared to placebo. This study is particularly notable since its careful inclusion criteria led to

selection of subjects with clear pre-capillary disease (average PVR of 5.8 WU, TPG of 27 mmHg, and DPG of 10 mmHg.), regardless of the definition used.

The recent clinical trials in both HFrEF-PH and HFpEF-PH remind us that the use of PAH-specific therapies in PH-LHD should only be in the context of clinical trials.

Conclusions and Future Directions

In recent years, there has been significant progress in the classification and characterization of PH-LHD including identification of a subset who merit special attention (CpcPH). The significance of accurate hemodynamic assessment for its diagnosis and prognosis cannot be overstated. Currently, there are currently no approved PH-specific therapies in the setting of LHD, and treatment efforts remain limited to targeting underlying left heart disease. Future research is needed to improve both hemodynamic and non-hemodynamic characterization of PH-LHD phenotypes as well as novel therapeutic strategies to target these populations.

Compliance with Ethical Standards

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