Under Pressure: Right Heart Catheterization and Provocative Testing for Diagnosing Pulmonary Hypertension

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ABSTRACT: Pulmonary hypertension (PH) is a heterogenous disorder involving multiple pathophysiological processes that ultimately affect the vasculature within the lungs. Right heart catheterization (RHC) continues to be the benchmark for diagnosing PH. The use of provocation techniques during RHC can help sub-characterize the type of PH and thus assist in developing appropriate treatment strategies for the management of each PH subtype. This review examines proven and novel approaches for evaluating the pulmonary vasculature during RHC and aspires to provide an accurate, clinically relevant framework for using RHC to diagnose and manage PH. Further improvement in standardized protocols will help optimize the application of RHC in patients with PH.

INTRODUCTION

Pulmonary hypertension (PH) is a clinical disorder involving multiple pathophysiological processes that ultimately affect the vasculature within the lungs. The World Health Organization (WHO) has grouped patients with PH into five distinct subgroups based on similar pathologic findings and hemodynamic profiles, which demonstrates the heterogenous nature of this disease (see related table on p. 9 in "Evaluation, Diagnosis, and Classification of Pulmonary Hypertension" by Beshay et al. in this issue).[1] It is important to recognize this concept because the management of PH is different for each subgroup.

The symptoms of PH are usually insidious, typically presenting as dyspnea on exertion. Patients can also develop abdominal distension and/or lower extremity edema with the onset of right ventricular (RV) failure. While echocardiogram findings such as an enlarged right atrium and RV, depressed RV systolic function, and elevated estimated pulmonary artery systolic pressure[2] can indicate the presence of PH, the gold standard for diagnosing PH is right heart catheterization (RHC).[1] Certain provocation techniques during RHC can lead to a clearer picture of cardiopulmonary hemodynamics and result in earlier diagnosis of cardiopulmonary disease while also affording better characterization of the PH subtype.

This review explores the role of provocative testing during RHC to offer a definitive diagnosis, determine disease severity, and identify the etiology of PH. The goal is to provide clinicians with a concise and clinically sound framework for improving the use of RHC in PH diagnosis and management.

RIGHT HEART CATHETERIZATION TO DIAGNOSE AND CLASSIFY PULMONARY HYPERTENSION

The purpose of RHC is to confirm the diagnosis of PH (class I, level of evidence C), determine its severity, identify the etiology to guide management (class I, level of evidence C), and assess vasoreactivity of the pulmonary vasculature (class IIa, level of evidence C).[1] Given the significant impact hemodynamic measurements have on the management of PH, all patients with PH should undergo a RHC, especially since the procedure itself has very low morbidity (1.1%) and mortality (0.055%).[3]

Right heart catheterization allows for accurate measurement of right atrial (RA) and ventricular (RV) pressures, pulmonary artery pressure (PAP) and mean PAP (mPAP), pulmonary capillary wedge pressure (PCWP), and venous oxygen saturation from the pulmonary artery (PA), as well as superior vena cava (SVC), inferior vena cava (IVC), RA, and RV oxygen saturations if a shunt is suspected.

Calculated measurements performed during RHC include (1) cardiac output (CO) and index (CI) by Fick equation or thermodilution, (2) systemic vascular resistance (SVR), (3) transpulmonary gradient (TPG), (4) diastolic pressure gradient (DPG), and (5) pulmonary vascular resistance (PVR). The CO and CI by Fick should be chosen over thermodilution if there is a suspected shunt since thermodilution may be inaccurate due to early circulation of the injectate. The shunt can be identified from a step-up in the venous oxygen saturations obtained from the SVC, IVC, RA, RV, and PA (also known as a shunt run).

The 6th World Symposium on PH recently defined PH as a resting mPAP > 20 mm Hg,[4] which is a change from the previous definition of mPAP > 25 mm Hg. However, this definition should

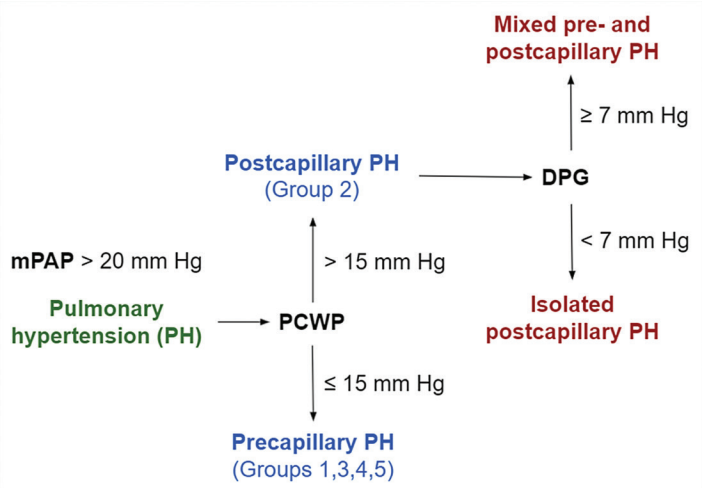

Figure 1.
Hemodynamic definitions of pulmonary hypertension (PH), including PH with left heart disease.

not be the sole diagnostic indicator of PH since there are several explanations for an elevated mPAP (eg, elevated PCWP, increased CO). From here, PH can be further divided into precapillary and postcapillary, with precapillary PH defined as a PCWP ≤ 15 mm Hg and postcapillary PH as a PCWP ≥ 15 mm Hg. Postcapillary PH can then be further categorized into isolated postcapillary PH when PVR < 3 Wood units (WU) and mixed pre- and postcapillary PH when PVR is elevated ≥ 3 WU (Figure 1).[5] It is our opinion that a DPG < 7 mm Hg or ≥ 7 mm Hg is also a simple and effective way to differentiate isolated postcapillary PH and mixed pre- and postcapillary PH, respectively, but use of the DPG is not part of the 6th World Symposium definitions. Finally, pulmonary arterial hypertension (PAH) is a subclassification of PH and on RHC is defined as precapillary PH with a PVR ≥ 3 WU (Table 1).[4] This is also seen with mixed pre- and postcapillary PH.

The hemodynamic waveforms can also provide additive information. In the presence of RV failure, the RA pressure will be significantly elevated. When contracting against elevated RV diastolic pressures, a prominent *a* wave is seen on the RA tracing. The RA waveform may display prominent *v* waves, suggesting severe tricuspid regurgitation, which is often seen with PH. Large v waves are also visible with decreased RA compliance from chronic elevated pressure.[6]

Normally, the RV functions in a low-impendence, high-capacitance, low-pressure system. It can easily accommodate increases in volume but is exquisitely sensitive to changes in afterload. In the early stages of PH, RV function is normal and can pump against an increase in pulmonary vascular resistance. As the RV fails, RV end-diastolic pressure rises. The RV waveform will show a sharp early diastolic dip followed by elevated and sustained diastolic pressure. A prominent *a* wave may also be seen, which reflects RV noncompliance.[6]

The PA systolic pressure (PASP) is elevated in PH and should equal the RV systolic pressure in the absence of pulmonic stenosis. PA diastolic pressure (PADP) is an indirect measurement of the LA pressure and LV end-diastolic pressure (LVEDP) in the absence of downstream pulmonary venous or mitral valve pathology. Thus, in postcapillary PH, PADP also will be elevated.

While PCWP and LVEDP are often used interchangeably to describe left-sided filling pressures, it is important to understand that they both provide different information. The mean PCWP provides an integrated measure of the hemodynamic burden imposed by the left atrial (and indirectly LV) operating compliance on the pulmonary circulation. In contrast, the LVEDP is a surrogate measure of LV pre-load and LV diastolic operating compliance alone.[7] The discrepancies between LVEDP-PCWP are particularly exaggerated in the presence of a large *v* wave as in mitral regurgitation or stiff LA syndrome, but also in mitral stenosis, pulmonary vein stenosis, and pulmonary veno-occlusive disease. Interestingly, the PCWP has been shown to have greater prognostic significance than

DEFINITION	HEMODYNAMIC CHARACTERISTICS	CLINICAL GROUPS
PH	mPAP > 20 mm Hg	All groups
Precapillary PH	mPAP > 20 mm Hg PCWP ≤ 15 mm Hg PVR ≥ 3 WU	PAH (group 1) Due to lung disease and/or hypoxia (group 2) Chronic thromboembolic disease (group 4) Unclear and/or multifactorial (group 5)
Postcapillary PH	mPAP > 20 mm Hg mPCWP > 15 mm Hg PVR < 3 WU	Due to left heart disease (group 4) Unclear and/or multifactorial (group 5)
Isolated postcapillary PH	mPAP > 20 mm Hg PCWP > 15 mm Hg DPG < 7 mm Hg* PVR ≤ 3 WU	
Mixed pre- and postcapillary PH	mPAP > 20 mm Hg PCWP > 15 mm Hg DPG ≥ 7 mm Hg* PVR ≥ 3 WU	

Table 1.
Hemodynamic profiles of pulmonary hypertension (PH). mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension; DPG: diastolic pulmonary gradient; WU: Wood units

*Not part of 6th World Symposium on Pulmonary Hypertension Definitions.[4]

LVEDP in patients with heart failure with preserved ejection fraction (HFpEF)[8] and thus must always be measured accurately. In fact, when trying to calculate pulmonary arteriolar resistance or evaluate the cause of dyspnea, clinicians should preferentially use the mean PCWP instead of the LVEDP.[7]

It is important to note that in the later stage of disease, severe PH with RV failure might demonstrate decreased PA pressures to near-normal levels and should not be mistaken for a lack of pathology. Rather, it is because the failing RV is unable to generate the expected pressures, and this is often accompanied by significantly elevated RA and RV end-diastolic pressures.[6]

As discussed earlier, a PCWP ≥ 15 mm Hg distinguishes between pre- and postcapillary PH. In cases of severe PH, hybrid tracings overestimating the wedge pressure are common. In such cases, PCWP can be confirmed with a wedge oxygen saturation (> 92%) or by measuring the LVEDP directly (assuming no mitral stenosis).

To complete the baseline hemodynamic assessment, CO should also be measured. Cardiac output is normal in patients who are well compensated, but it decreases as RV failure worsens, so patients can develop cardiogenic shock. Regardless of the underlying cause of PH, RV failure ultimately leads to hemodynamic deterioration and death. Hence, RV dysfunction is a harbinger of mortality in patients with PH.

RIGHT HEART CATHETERIZATION BEST PRACTICES TO AVOID MISDIAGNOSIS

Because it is technically demanding, RHC requires expertise and painstaking precision to obtain accurate and clinically relevant information. Incorrect measurement or interpretation of hemodynamic tracings will result in diagnostic inaccuracies and inappropriate treatment. There is evidence that RHC should only be done at expert centers (class I, level of evidence B) to avoid the aforementioned scenarios.[1,3] In fact, the RePHerral study (A Multi-Center Study Of The Referral Of Pulmonary Hypertension Patients To Tertiary Pulmonary Hypertension Centers) demonstrated that patients referred to PH centers for diagnosis and treatment were often initially misdiagnosed or misclassified and frequently given inappropriate medications as a result.[9] Overall, 42% of patients (25 of 59) who were referred to a tertiary care center for RHC were ultimately diagnosed with something other than their initial PH diagnosis. Furthermore, out of the 56 patients with a prereferral diagnosis of PAH, only 41 had confirmed PAH while the other 7 showed no evidence of PH after tertiary care evaluation. Moreover, 57% of these patients had been prescribed medications that were not within guideline recommendations.[9]

To ensure accurate hemodynamic measurements when performing RHC, particular attention should be paid to the following:

(1) The external pressure transducer should be zeroed at the mid-thoracic line in a supine patient. This represents the level of the left atrium.
(2) All pressure measurements should be determined at end expiration.[10]
(3) The PCWP should be verified with a wedge oxygen saturation or by measuring the LVEDP directly in all cases where it is uncertain if the hemodynamic tracing represents a true wedge.
(4) Cardiac output should be obtained using both thermodilution and Fick, and the more reliable value should be used (Fick when there is severe tricuspid regurgitation, and thermodilution in the presence of intracardiac shunts).
(5) Noninvasive blood pressure should be recorded at the time of the procedure.

PULMONARY VASOREACTIVITY TESTING DURING RIGHT HEART CATHETERIZATION

Pulmonary vasoreactivity testing can determine if a patient is suitable for treatment with a high-dose calcium channel blocker (CCB), and it is recommended only for those with idiopathic, heritable, or drug-induced PAH (WHO group 1 PH with mPAP > 20 mm Hg, PCWP ≤ 15 mm Hg, PVR ≥ 3 WU). These responders have improved survival over other forms of PAH.[1] In all other forms of PAH and PH, the response is inadequate and/or the drug is not indicated.

During testing, the patient typically receives pure oxygen for 5 minutes. If PA pressures normalize with supplemental oxygen alone (indicating hypoxic vasoconstriction), further vasoreactivity testing is unnecessary and the patient should be treated with oxygen therapy. If the patient does not respond to oxygen therapy, one should proceed with acute vasoreactivity testing. The US-based expert consensus document on PH observes the use of inhaled nitric oxide, intravenous adenosine, and intravenous epoprostenol for vasoreactivity testing, while the European guidelines also recognize inhaled iloprost. Contraindications include patients with WHO group 2 PH, significant LV failure, or severe hypertension due to a significantly elevated risk of pulmonary edema as well as patients with suspicion of pulmonary veno-occlusive disease.

The American College of Cardiology Foundation/American Heart Association expert consensus on PH recommend inhaled nitric oxide as the preferred agent due to its short half-life and minimal side effects. With the assistance of a respiratory therapist, the patient is administered 40 ppm of nitric oxide with 100% oxygen through a mask (the literature has reported doses up to 80 ppm).[11,12] Hemodynamic measurements are made at baseline

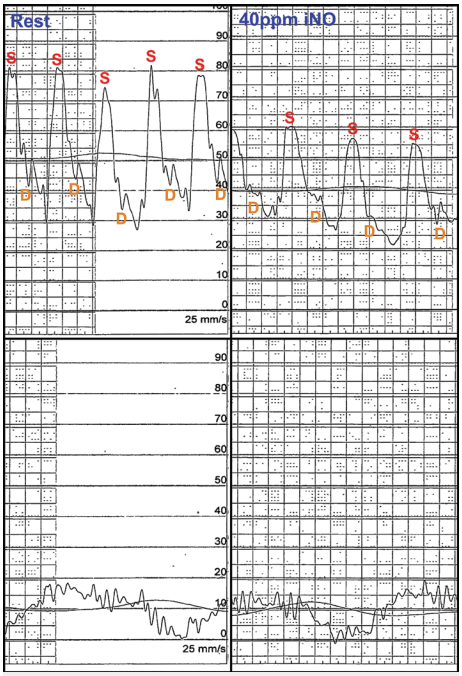

Figure 2.
Hemodynamic tracings of pulmonary arterial hypertension with a positive vasoreactivity test using inhaled nitric oxide (see Table 2).

	PA (mm Hg)	PCWP (mm Hg)	TPG (mm Hg)	PVR (WU)	CO/CI (THERMODILUTION)
Rest	82/34 (50)	10	40	9	4.7/2.4
Nitric oxide 40 ppm for 5 minutes	58/27 (37)	11	26	5	5.1/2.6

Table 2.
An example of a positive vasoreactivity test for pulmonary arterial hypertension. Hemodynamic measurements at rest are consistent with severe pulmonary arterial hypertension. Positive vasoreactivity test with 40 ppm inhaled nitric oxide demonstrating an absolute decrease in mean pulmonary artery pressure (mPAP) by 13 mm Hg and a final mPAP of 37 mm Hg. Pulmonary vascular resistance (PVR) improved from 9 Wood units (WU) to 5 WU. See Figure 2 for hemodynamic tracings. The patient was treated with high-dose nifedipine with significant and sustained improvement in her PVR and symptoms. PA: pulmonary artery; PCWP: pulmonary capillary wedge pressure; TPG: transpulmonary gradient; CO/CI: cardiac output/cardiac index

and after 5 to 10 minutes of continuous inhaled nitric oxide.

As an alternative, epoprostenol can be infused intravenously starting at 2 ng/kg/min and is increased by 2 ng/kg/min every 10 to 15 minutes until a maximum dose of 12 ng/kg/min is reached.[11] Side effects are more commonly encountered with epoprostenol and include flushing, headache, nausea/vomiting, and hypotension. It is cheaper than inhaled nitric oxide.

Adenosine is also infused intravenously at 50 mcg/kg/min and increased by 50 mcg/kg/min until a maximum dosage of 250 to 350 mcg/kg/min is achieved, although some studies have used a maximum dosage of 500 mcg/kg/min.[13] Side effects of adenosine include bradycardia, heart blocks, chest pain, dyspnea, and hypotension and can be severe enough that the target dosage might not be reached.

Iloprost is administered via a "rain drop" nebulizer circuit, with 50 mcg diluted in 5 mL of 0.9% normal saline given at an initial dose of 2.5 mcg and increasing to a maximum dose of 5 mcg.[14] Since iloprost has a significantly longer half-life (up to 30 minutes) compared with epoprostenol (up to 6 minutes), hemodynamic measurements are typically repeated at least 30 minutes after drug administration.[11]

A positive vasodilator response is defined as a decrease in mPAP from ≥ 10 mm Hg to ≤ 40 mm Hg without a decrease in CO (Table 2, Figure 2).[4] A noticeable spike in mean PCWP during acute vasodilator testing is suggestive of left heart disease (WHO group 2 PH). In general, positive vasodilator testing is seen in about 12.6% of patients with idiopathic PAH (and as high as 26% in other studies); of these patients, only about half (6.8%) had a long-term response to CCBs.[15] Acute responders should be treated with high-dose, long-acting CCBs such as nifedipine, diltiazem, or amlodipine.

VASODILATOR CHALLENGE DURING RIGHT HEART CATHETERIZATION

The role of intravenous nitroglycerin and sodium nitroprusside during RHC is to distinguish patients who have true mixed-etiology PH from patients who have WHO group 2 PH with falsely elevated TPG or PVR in the setting of elevated PCWP. Typically, using an invasive arterial line, the mean arterial pressure (MAP) should be decreased to a goal of 65 mm Hg via titration of these intravenous vasodilators followed by repeat hemodynamic measurements. If the TPG and PVR normalize after reducing the mPAP and PCWP, these patients do not have true mixed-etiology PH but rather WHO group 2 PH with a reactive precapillary component. Because PCWP, mPAP, and MAP respond better to nitroglycerin and sodium nitroprusside, these agents should be used for provocative testing in these cases rather than pure pulmonary vasodilators, which are superior in reducing PVR and hence are more appropriate for use in vasoreactivity testing.[16]

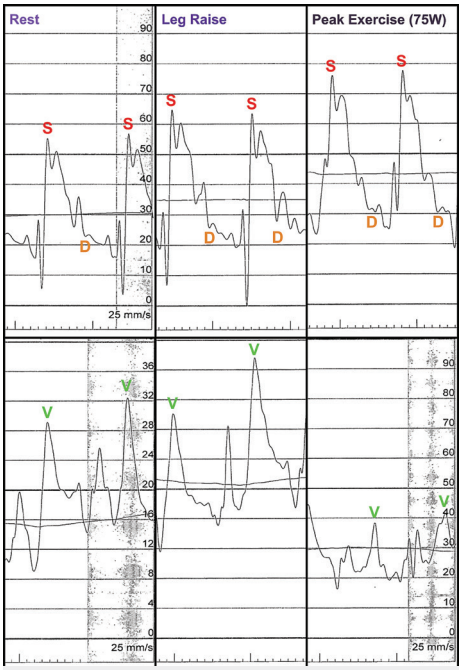

Figure 3.
Hemodynamic tracings of World Health Organization group 2 pulmonary hypertension due to occult heart failure with preserved ejection fraction (HFpEF) that was unmasked with exercise (see Table 3).

	PA (mm Hg)	PCWP (mm HG)	TPG/DPG (mm Hg)	PVR (WU)	CO/CI (THERMODILUTION)
Rest	54/20 (31)	14	17/6	3	5.3/2.9
Passive leg raise	62/24 (37)	20	17/4		-
Peak exercise (75 watts)	75/30 (45)	30 (*v* wave 40)	15/0	2	7.8/4.4

Table 3.
An example of World Health Organization (WHO) group 2 pulmonary hypertension (PH) due to occult heart failure with preserved ejection fraction (HFpEF) that was unmasked with exercise (exercise-induced HFpEF). Hemodynamics at rest suggest mildly elevated left-sided filling pressures and mild pulmonary hypertension (PH) with preserved cardiac index (CI). With passive leg raise, mean pulmonary artery pressure (mPAP) and pulmonary capillary wedge pressure (PCWP) increase significantly, consistent with group 2 PH. With supine bicycle exercise, at peak exercise (75 watts), hemodynamics confirmed severe WHO group 2 PH with an mPAP of 45 mm Hg and PCWP of 30 mm Hg with a transpulmonary gradient (TPG) of 15 mm Hg and a diastolic pulmonary gradient (DPG) of 0 mm Hg. See Figure 3 for hemodynamic tracings. The patient was treated with diuretics and spironolactone with significant and sustained improvement in her dyspnea.
PA: pulmonary artery; PVR: pulmonary vascular resistance; CO/CI: cardiac output/cardiac index

EXERCISE TESTING DURING RIGHT HEART CATHETERIZATION

Exercise testing is another provocative technique that uses the left heart response to refine the diagnosis between exercise-induced PAH versus occult WHO group 2 PH related to HFpEF, also referred to as exercise-induced HFpEF. A resting RHC may be inadequate for patients with activity-related dyspnea and an mPAP of < 20 mm Hg. During exercise, the PCWP increases with the increase in CO. In healthy adults, the slope of this relationship does not exceed 2 mm Hg/L/min.[17-19] This threshold remains intact if exercise is sustained for > 3 minutes beyond the early peak in PCWP that can be seen with older individuals.[19] Similarly, the normal mPAP response to exercise in healthy people does not exceed 3 mm Hg/L/min.[20] This can be taken a step further with invasive cardiopulmonary exercise testing, which measures expired gas while assessing pressure, flow, and resistance from RHC.[21]

Exercise testing is indicated when the etiology of dyspnea is unclear and when the patient's symptoms are disproportionate to the degree of cardiac or pulmonary disease. It is especially useful in revealing occult pulmonary vascular and/or left heart disease in patients suspected of having PH or with borderline hemodynamics (ie, PCWP 12-15 mm Hg and/or PVR ~ 3 WU).[22] Finally, exercise testing is useful in assessing the degree of RV contractile reserve and can assist with determining prognosis and treatment escalation.[23,24]

Dynamic exercise is performed using stationary cycle ergometers with electronic brakes, mounted on the catheterization lab table. Exercise protocols vary significantly between institutions but should be standardized in each catheterization lab. Three minutes per stage is ideal to achieve steady state oxygen uptake, with a goal of 10 minutes exercise duration.[25] Both peak and immediate postexercise measurements are vital since vascular pressures recover quickly after exercise.[26] At our institution, using a Verrata pressure wire (the same wire used to measure instantaneous wave-free ratio for evaluation of coronary physiology) has helped provide more accurate measurements; these are independent of the "whip" that is often seen with the Swan-Ganz catheter due to displacement, motion artifact, and respiratory swings. Oxygen consumption for Fick calculation of exercise CO should be directly measured and not estimated. This is important because the estimated oxygen consumption (at rest) used to calculate the Fick cannot be accurately adjusted for exercise states and, therefore, would result in a falsely low CO. If direct measurement of maximum oxygen consumption (VO_2 max) via specialized equipment is not available, as is the case in many labs, then thermodilution should be used instead as a reasonable alternative.

Hemodynamic criteria supporting the diagnosis of exercise-induced PAH

includes an mPAP > 30 mm Hg with total pulmonary vascular resistance > 3 WU at maximal exercise, especially if peak CO is less than 10 L/min. This has a reported diagnostic sensitivity and specificity of 0.93 and 1, respectively.[27] The PCWP usually remains normal (≤ 12 mm Hg). Other criteria include a linearized slope of multiple mPAP and CO determinations > 3 WU[26,28] and a change in peak minus resting mPAP over the respective change in CO > 3 WU, but these are less sensitive.[28,29]

The diagnosis of WHO group 2 PH related to occult HFpEF is supported by a PCWP ≥ 15 mm Hg at rest or an increase in PCWP to ≥ 25 mm Hg at peak physical activity, ideally along with ΔPCWP/ΔCO slope > 2 mm Hg/L/min (Table 3, Figure 3). The pathophysiology is due to decreased LV compliance resulting in an increase in PCWP.[30] A ratio of PCWP over workload normalized to body weight > 25.5 mm Hg/W/Kg has been associated with occult HFpEF.[28,31] In general, unless mixed-etiology PH is present, patients with occult HFpEF have normal PVR at rest and PVR that typically does not exceed 1.5 WU at peak activity. Importantly, chronic HFpEF may result in adverse remodeling of pulmonary vasculature and abnormal pulmonary vascular reactivity; in this case, PVR would increase both at rest and with exercise.

RAPID FLUID CHALLENGE DURING RIGHT HEART CATHETERIZATION

A rapid fluid challenge with saline loading increases both venous return to the heart and LVEDP, thereby unmasking HFpEF in patients with decreased LV compliance (WHO group 2 PH). This is valuable for identifying occult HFpEF in high-risk patients (eg, those with obesity or scleroderma) and accurately classifying patients with ambiguous phenotypic characteristics that overlap between WHO group 1 and group 2 PH.[29] Additionally, a saline-loading fluid challenge is widely available, inexpensive, and easily administered, with 500 mL of 0.9% sodium chloride infused intravenously over 5 minutes. Slow infusion should be avoided since it would enable fluid redistribution in the interstitial space and, therefore, a false negative result.

In general, healthy individuals maintain a PCWP < 15 mm Hg after rapid saline infusion,[32] but those with HFpEF will have a steeper rise in PCWP (≥ 18 mm Hg), which is indicative of WHO group 2 PH.[33] Unlike exercise, saline loading has minimal effect on heart rate or blood pressure. Theoretically, this means that ventricular compliance is the only variable being tested.[25] However, exercise testing increases both heart rate and contractility, thus increasing myocardial wall stress and oxygen demand. By this virtue, it may be more sensitive than saline loading in detecting occult WHO group 2 PH.[34] Even so, if exercise testing is not available, saline loading is a suitable and perhaps more reliable provocative test to identify WHO group 2 PH (occult HFpEF) in patients who already have an intermediate to high pretest probability of the disease.[35]

OTHER PROVOCATIVE TESTS AND FUTURE DIRECTIONS

Passive leg raise increases cardiac preload by about 300 to 500 mL through return of blood from the lower extremity venous system. It is almost analogous to saline loading except that the load increase is not accurately defined. This simple technique involves raising the patient's lower extremities to 45 degrees using a wedge and repeating hemodynamic measurements a minute later (since the effects can rapidly dissipate). However, this requires further validation since there is no current consensus if PCWP ≥ 18 mm Hg can be definitively used to diagnose occult HFpEF (WHO group 2 PH).

Another technique involves the use of an esophageal balloon to determine the relationship between intrathoracic pressure and pulmonary hemodynamics. This is especially useful in obese patients. In a study by Jawad et al., unadjusted PCWP resulted in misclassifying up to 33% of patients with postcapillary PH because intrathoracic pressure changes had no impact on their PVR.[36] More research is needed to validate this technique.

In dialysis-dependent patients, AV fistulae can sometimes cause high CO heart failure and/or PH, especially when fistula flow increases ≥ 1.5 L/min or the ratio of fistula flow to CO is ≥ 20%. To determine this, hemodynamic measurements are taken at baseline and after occlusion of the AV fistula using either digital compression or an inflated blood pressure cuff. This decreases the preload and reduces both CO and mPAP. Temporary compression in those with pre- and/or postcapillary PH can reveal the effect of elevated CO on mPAP but cannot determine the precise impact on PCWP and PVR.[37]

Finally, inotropes have also been shown to be useful in provocative testing for PH. Dobutamine infusion has been used to assess pulmonary vasodilatory and RV contractility reserve, especially in patients who cannot exercise. Dobutamine is infused intravenously starting at 5 mcg/kg/min and is increased to 10, 20, 30, and 40 mcg/kg/min at 3-minute intervals to reach the maximum dose. Others have used a predefined target heart rate (eg, 120 bpm). An increase in mPAP that is disproportionate to the increase in CO indicates decreased pulmonary vasodilatory reserve.[38] Sharma et al. were also able to assess reduced right ventricular contractile reserve in patients with PAH using low-dose dobutamine stress echocardiography.[39] Meanwhile, Givertz et al. have shown that an intravenous bolus of milrinone (50 µg/kg) consistently decreases PVR in patients with PH secondary to severe left-sided heart failure.[40]

The mechanism of action may be due to a direct pulmonary vasodilator effect or to a secondary effect due to an increase in CO, or more likely both. Thus, its value lies in being able to assess for PH reversibility in patients undergoing evaluation for heart transplantation. It should be noted, however, that the sample size of this study was small (n = 27), with no follow-up after transplantation and therefore no conclusions can be drawn regarding the predictive value of the milrinone response for posttransplantation events.[40]

CONCLUSION

RHC remains the gold standard modality that provides a definitive diagnosis, determines severity, and identifies the etiology of PH, thus enabling guided clinical decision making and early and appropriate therapeutic intervention. The astute clinician must determine which provocative technique will balance efficacy, cost, and safety while refining the diagnosis and assessing early pathology before symptoms manifest and irreversible remodeling of the pulmonary vasculature occurs. Provocative testing should also be performed whenever there is an ambiguous PH phenotype or unexplained dyspnea but with normal or borderline pulmonary pressures. Finally, given the complexity of RHC, there may be value in performing this procedure only in expert centers. Further improvement in standardized RHC protocols for PH will help achieve optimal application of RHC for the diagnosis and management of PH in routine clinical practice.

KEY POINTS

- Right heart catheterization remains the gold standard modality for definitive diagnosing of pulmonary hypertension (PH) while also determining severity and identifying the etiology of PH. This allows uncompromising guided clinical decision making and early and appropriate therapeutic intervention.
- Accurate hemodynamic measurements are crucial to avoid misdiagnosis, and this includes zeroing the external pressure transducer prior to the procedure, obtaining hemodynamic measurements at end expiration, verifying the pulmonary capillary wedge pressure in all cases where it is uncertain, and obtaining a cardiac output using the more reliable method of thermodilution or Fick, depending on the clinical scenario.
- There are multiple provocative techniques available to refine the diagnosis of PH. The astute clinician must balance efficacy, cost, and safety when deciding which provocative test is appropriate for the patient.
- Provocative testing should be performed whenever there is an ambiguous PH phenotype or unexplained dyspnea but with normal or borderline pulmonary pressures.

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