The Pulmonary Hypertension Association will soon release its second interactive CD-ROM designed to assist practicing clinicians in their management of patients with pulmonary hypertension. This CD-ROM will present a series of case vignettes allowing clinicians to test their knowledge regarding the diagnosis and treatment of various manifestations of pulmonary hypertension. It will provide the opportunity to work through each case, selecting studies to view and then highlighting the salient features of these tests. The clinician will then be able to pick treatment options for the patient. Throughout each case questions regarding management will be posed, followed by suggestions and responses from international experts in the field of pulmonary hypertension. This CD-ROM will be an excellent resource for practitioners interested in expanding their knowledge of the management of patients with pulmonary arterial hypertension.

Pulmonary Venous Hypertension: A Diagnostic and Therapeutic Dilemma

Francisco J. Soto, MD, MS
Assistant Professor
Director, Pulmonary Hypertension Program
Medical College of Wisconsin
Milwaukee, Wisconsin

Introduction

Current data suggest that patients with pulmonary arterial hypertension (PAH)—those with involvement of the pulmonary circulation at the precapillary level—can experience a significant clinical and hemodynamic benefit from available treatments such as prostacyclin, endothelin-receptor antagonists, or phosphodiesterase-5 inhibitors.[1] Data are lacking as to whether other categories of pulmonary hypertension,[2] such as pulmonary venous hypertension (PVH), which involves the pulmonary circulation at the postcapillary level, enjoy a similar treatment benefit. It is even possible that those with PVH may experience worsening of their symptoms when such therapies are administered by increasing the left-sided filling volume and pressure.

Based on current guidelines,[3] a diagnosis of PAH is established once a resting mean pulmonary arterial pressure (mPAP) greater than 25 mmHg and a left atrial or left ventricular pressure of 15 mmHg or less is documented. On the other hand, the same mPAP value cutoff in the presence of left-sided pressure greater than 15 mmHg would fulfill the definition of PVH. Such simple distinction criteria based on left-sided filling pressures is helpful in discriminating between clear cut cases of PAH and PVH. Unfortunately, clinicians are frequently faced with more complex diagnostic case scenarios that require additional workup and interventions. One such case is presented here to provide some diagnostic insights that may help better discriminate between the two categories.

Key Words—Pulmonary venous hypertension diagnosis, pulmonary arterial hypertension, right heart catheterization, left heart catheterization, LVEDP.

Address for reprint requests and other correspondence: Francisco J. Soto, MD, Director, Pulmonary Hypertension Program, Medical College of Wisconsin, 9200 West Wisconsin Avenue, Suite 5200, Milwaukee, WI 53226, HYPERLINK "mailto:fsoto@mcw.edu" fsoto@mcw.edu.

Case Description

The patient is a 62-year-old woman with a past medical history significant for 20 years of systemic hypertension (**Table 1**). She was referred to our pulmonary hypertension program for progressive dyspnea on exertion and an echocardiogram that suggested the presence of pulmonary hypertension. Her primary physician ordered the test based on her complaints of 2 years of progressive dyspnea on exertion that was not clearly explained by other etiologies. Her outside echocardiogram revealed an estimated right ventricular systolic pressure of at least 54 mmHg (estimated right atrial pressure 5 mmHg). A thorough evaluation and diagnostic workup (**Table 2**) was performed at our institution. These tests were unremarkable for such secondary causes of pulmonary hypertension as thromboembolic disease, parenchymal lung disease, congenital heart disease, and collagen vascular disease. Transthoracic echocardiography (**Figure 1**) with a specific pulmonary hypertension protocol was repeated at our institution and confirmed the outside echocardiographic findings (**Table 2**).

Clinical suspicion for idiopathic PAH was present in her case based on a negative workup for secondary causes. However, her age, her long history of systemic hypertension, and her echocardiographic findings, including left-sided changes plus unremarkable right-cardiac structures, raised suspicion also for undetected left heart disease in the form of left ventricular diastolic dysfunction. This entity can lead

Table 1. Baseline Demographics.

Age and gender	62-year-old woman
Symptoms	Dyspnea on exertion (DOE) by walking less than ½ mile (down from being able to walk more than 2 miles one year earlier) Walks at slower pace now; DOE by climbing one flight of stairs (no trouble with this activity one year earlier) Bending over leads to dyspnea Describes occasional palpitations; no chest pain or lightheadedness with activity No orthopnea or paroxysmal nocturnal dyspnea Mild progressive leg swelling despite diuretic use WHO functional class III
Medical history	Systemic hypertension (20-year history) Mild coronary artery disease (medical management) Less than 10 pack-year smoking history (quit over 30 years ago) No alcohol, illicit-drug, or diet pill intake Family history of coronary artery disease
Medications	Calcium-channel blocker Angiotensin-receptor blocker/hydrochlorothiazide combination Loop diuretic Statin Low-dose estrogen replacement therapy
Relevant physical examination findings	Blood pressure 171/100 mmHg Heart rate 80 beats per minute Respiratory rate 20 breaths per minute Oxygen saturation 98% (room air) Jugular venous pressure 6 cm above right clavicle at 45° angle Normal breathing sounds Regular heart rhythm; softly accentuated P2; no murmur appreciated No right ventricular heave appreciated Mild peripheral edema

Table 2. Relevant Pulmonary Hypertension Workup.

Laboratory analysis	Cell blood count, basic chemistry, liver function, thyroid function test results within normal limits HIV test nonreactive ANA negative BNP 81
Computed tomographic scan of chest with pulmonary embolism protocol and lower extremity venous system enhancement	Enlarged cardiac size Mildly enlarged pulmonary artery Normal lung parenchyma No evidence of pulmonary embolism or deep vein thrombosis
Overnight polysomnography	No evidence of sleep-related breathing disorder (apnea-hypopnea index less than 5 events per hour)
Pulmonary function tests	Normal resting spirometry and lung volumes Flow volume loop normal Predicted DLCO 74%; increased to 102% after adjustment for alveolar ventilation
Transthoracic echocardiography	Normal left ventricular ejection fraction No evidence of diastolic dysfunction Mild left ventricular hypertrophy Normal right atrial size Borderline normal-mild left atrial enlargement Normal right ventricular size/function Estimated pulmonary artery systolic pressure 55 mmHg

to PVH and generate symptoms and findings similar to those in PAH. The lack of right-sided abnormalities on echocardiography certainly mitigates strongly against PAH. In general, one would expect to see some right-sided strain findings after 2 years of progressive dyspnea if PAH were to be the explanation for her symptoms.

She subsequently underwent diagnostic right and left cardiac catheterization at our institution (**Table 3**) to confirm the presence of pulmonary hypertension and to obtain additional hemodynamic data that could help discriminate between PAH and PVH. Her right heart catheterization numbers were consistent with a diagnosis of PAH given her elevated mPAP and a pulmonary capillary wedge pressure (PCWP) of 15 mmHg or less (**Figures 2** and **3**). However, a simultaneous left ventricular end-diastolic pressure (LVEDP) measurement—a number that is routinely obtained at our institution during initial diagnostic catheterizations[4]—was elevated at 22 mmHg. Her baseline PCWP forms did reveal a prominent v wave, something that can be found in the presence of mitral regurgitation or in impaired relaxation of the left ventricle. None of the two echocardiograms revealed evidence of significant mitral valve disease.

After reviewing her right heart catheterization numbers, we decided to perform an intravenous epoprostenol vasodilator trial to assess for the presence of vasoreactivity (**Table 3**). This led to only a minimal decrease in mPAP consistent with a negative vasodilator trial.

An exercise challenge was also conducted based on the suspicion for left heart disease trying to unmask impaired relaxation of the left ventricle. A 5-minute upper body exercise protocol, a flat dumbbell fly routine, led to a significant increase in pulmonary pressures with a concomitant LVEDP increase (**Table 3**).

Based on the presence of an elevated LVEDP, long-standing systemic hypertension history, plus the hemodynamic response observed during an exercise challenge, the suspicion for PVH remained strong in her case. We then proceed-

Table 3. Results of Cardiac Catheterization, Exercise Challenge, Vasodilator Trial, and Nitroprusside.

	Baseline	Exercise challenge	Intravenous epoprostenol trial (12 ng/kg/min)	Nitroprusside (1 mcg/kg/min)
Right atrial pressure (mmHg)	9			
Right ventricular pressure (mmHg)	55 systolic 5 diastolic 12 end			
Pulmonary artery pressure (mmHg)	55 systolic 22 diastolic 35 mean	74 systolic 35 diastolic 48 mean	51 systolic 20 diastolic 33 mean	34 systolic 10 diastolic 17 mean
Pulmonary capillary wedge pressure (mmHg)	15	28	22	7
Left ventricular end-diastolic pressure (mmHg)	22	32	22	8
Cardiac output/Cardiac index (L/min)/(L/min/m^2)	6.7/3.3		10.1/5.0	
Aortic systolic blood pressure (mmHg)	160	195	Low 140s	Low 120s

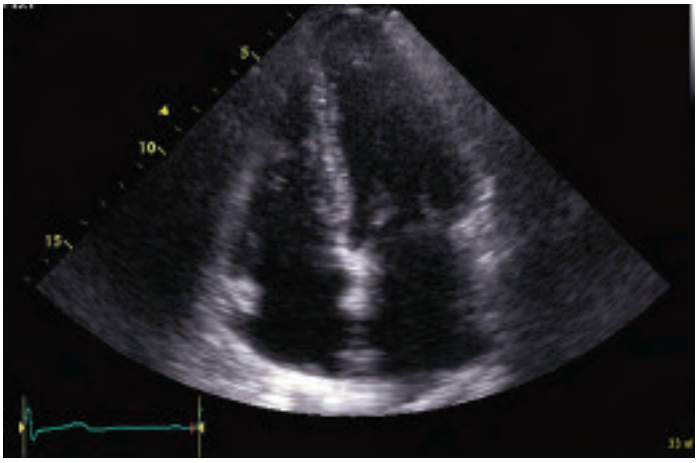

Figure 1. Four-chamber apical view on transthoracic echocardiography. Normal right and left ventricular chamber size. Normal right atrium size. Borderline normal-mild left atrium enlargement.

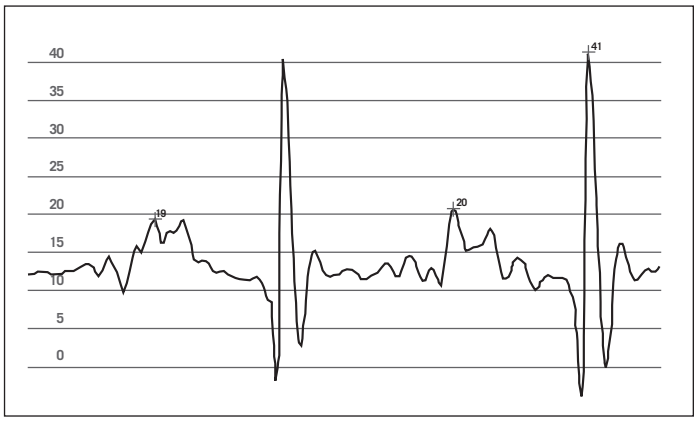

Figure 2. Sample tracing: mean pulmonary capillary wedge pressure at baseline. Peak a wave 20; mean a wave 15; v wave 40. Electronic mean reported as 13. All pressures reported as mmHg.

ed with an intravenous nitroprusside infusion at a starting dose of 1 mc/kg/min.[5] Our goal was to decrease her systemic systolic blood pressure (to around 100 to 110 mmHg) and/or decrease her LVEDP to less than 15 mmHg while simultaneously monitoring for pulmonary artery pressure changes. A pig tail catheter was kept in the left ventricle during the nitroprusside infusion to directly follow the left ventricular systolic pressure and the LVEDP.[5] Once the LVEDP and systemic systolic blood pressure normalized, a dramatic improvement in pulmonary arterial pressures was documented (**Table 3**). Right heart catheterization numbers revealed complete normalization of her pressures (**Figure 4**).

With the above hemodynamic findings plus a strong clinical suspicion for postcapillary pulmonary hypertension, her case was labeled as PVH secondary to left ventricular diastolic dysfunction. In an attempt to replicate the vascular effects of nitroprusside in the outpatient setting (direct preload and afterload reduction), treatment was started with a combination regimen of oral nitrates and hydralazine. Doses of these two agents were escalated during a period of several weeks aiming to reach a systemic systolic blood pressure in the 100 to 110 mmHg range as tolerated by side effects.

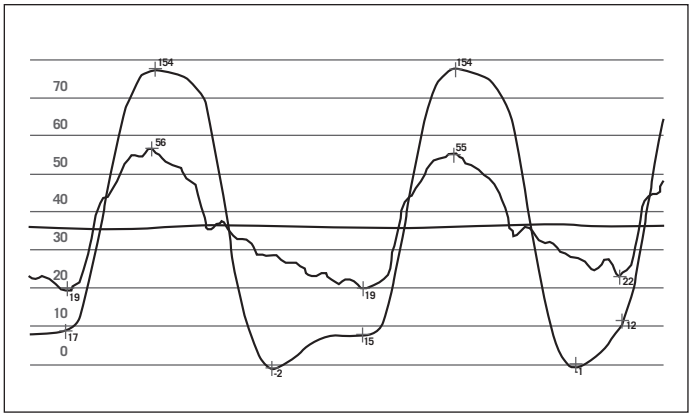

Figure 3. Sample tracing: pulmonary artery pressure (PAP) and left ventricular end-diastolic pressure (LVEDP) at baseline. Left ventricular systolic pressure: 154; LVEDP: 22; PAP: systolic 55, diastolic 22, mean 35. All pressures reported as mmHg.

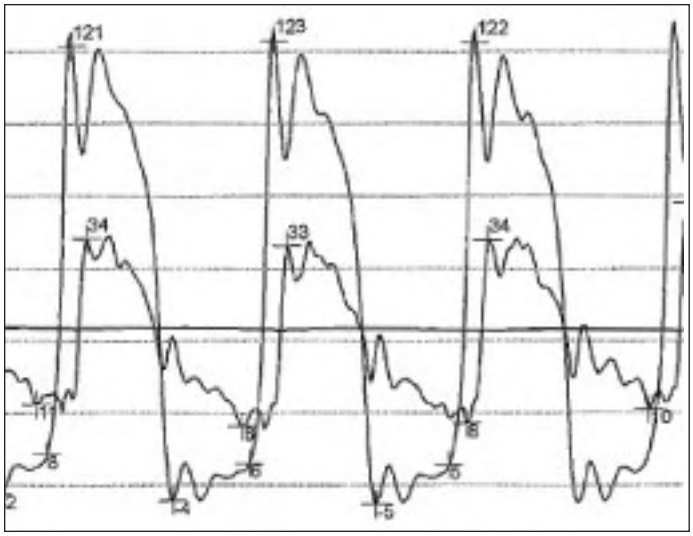

Figure 4. Sample tracing: pulmonary artery pressure (PAP) and left ventricular end-diastolic pressure (LVEDP) after nitroprusside. PAP: systolic 34, diastolic 10, mean 17; LVEDP: 8-10. All pressures reported as mmHg.

Diuretics were also up-titrated to achieve additional reduction in preload. We continued her other antihypertensive agents.

Follow-up

After more than 2 years from her cardiac catheterization and initiation of this therapeutic approach, the patient has continued to tolerate this regimen well without significant side effects. Her diuretics regimen has been adjusted based on a close follow-up of her brain natriuretic peptide (BNP) numbers and basic chemistry.

We have documented improvement between her baseline data and the most recent follow-up 2 and a half years later. Her BNP level decreased from 86 pg/mL at baseline to 42. Her functional status improved from a baseline World Health Organization (WHO) functional class III to an early II (mainly bothered by going up inclines and bending over). Her 6-minute walk test distance improved from 398 to 450 meters. Echocardiographic values have remained stable. No evidence of right ventricular dysfunction or dilatation has been documented. She has not experienced any signs of clinical deterioration throughout her follow-up visits (conducted approximately every 4 months). Given her stable clinical course, we have not introduced any pulmonary vasodilator agents to her regimen.

Discussion

Our case represents a common scenario that most physicians treating pulmonary hypertension currently face in their practice. Based on the increased awareness of pulmonary hypertension in the general public and health providers, large numbers of patients are being referred to be evaluated on the basis of dyspnea and an elevated pulmonary artery pressure on echocardiography. Many of these patients are older individuals with comorbidities such as systemic hypertension, diabetes mellitus, coronary artery disease, or obstructive sleep apnea. While some of them could and will have PAH, patients with those characteristics are more likely to have left ventricular diastolic dysfunction manifesting itself as PVH. Accordingly, given their underlying symptoms, a thorough evaluation is frequently indicated.

Since the available therapies to treat PAH are not only expensive but also may potentially worsen the symptoms in patients with PVH, it is very important to establish the proper diagnosis. To our knowledge, besides the use of a left ventricular filling pressure cutoff (> or ≤15 mmHg), there are no standardized protocols that allow the clinician to clearly discriminate between a diagnosis of PAH (especially idiopathic PAH) and PVH in complex cases like the one presented here.

Utilization of some of the interventions described above has allowed our group to better assess the more difficult cases. However, until any of these interventions is prospectively validated in large clinical trials, our practice is to have a very close follow-up for the first 6 to 12 months (or longer) on those patients being labeled as PVH to make sure that there are no obvious clinical, echocardiographic, or hemodynamic signs of deterioration. When in doubt, we promptly proceed with a repeat cardiac catheterization to assess cardiopulmonary hemodynamics in more detail.

With regard to the therapeutic management of pulmonary hypertension in the presence of left ventricular diastolic dysfunction, especially when the diastolic dysfunction can not be completely attributed to systemic hypertension, it is not clear whether PAH therapies could play a role. Some benefit has been suggested through anecdotal description in small case series. It will be interesting to see whether a potential benefit of these drugs in improving myocardial relaxation can overcome the likely increase in right-to-left blood flow that may result from their pulmonary vasodilation properties. This issue is under investigation at this time.[6]

Given the potential for abrupt systemic vasodilation, it is our practice to perform nitroprusside vasodilator trials while simultaneously monitoring LVEDP and systemic arterial pressures. In general, we would recommend avoiding nitroprusside trials in obvious PAH cases or those with significant right ventricular impairment since those patients might have an impaired hemodynamic response and not be able to adequately increase their cardiac output in the event of systemic hypotension. If left ventricular diastolic dysfunction is sus-

pected in these types of cases, other safer alternatives such as an exercise challenge or a fluid bolus could be considered in order to evaluate the left ventricular pressure response to extra volume or an increase in blood flow. Unfortunately, none of those interventions has been validated either.

Finally, our case also illustrates the value of measuring both PCWP and LVEDP during the initial diagnostic catheterization, especially in those patients with comorbidities that can lead to PVH. Important discrepancies between the two hemodynamic measurements can occur. If present, they could significantly alter the therapeutic approach and will have important implications on establishing the long-term prognosis of these patients. In addition, we recommend following the available guidelines for interpretation of hemodynamic tracings and pressure measurement.[7] The electronic mean measurements provided by catheterization laboratory software programs might not be completely accurate and could lead to initiation of therapies that are not clinically indicated. ■

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