Diagnostic Dilemmas: Diastolic Heart Failure Causing Pulmonary Hypertension and Pulmonary Hypertension Causing Diastolic Dysfunction


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Left heart disease can cause pulmonary hypertension via multiple mechanisms. In the past, a normal ejection fraction and the absence of left-sided valve disease or congenital heart disease provided reassurance that pulmonary hypertension was not related to left-sided heart disease. However, it is now recognized that patients with clinical heart failure commonly have a normal ejection fraction, a syndrome referred to as diastolic heart failure or heart failure with normal ejection fraction.[1,2] As reviewed below, the pathophysiologic mechanisms present in patients with diastolic heart failure may be heterogeneous. Although pulmonary hypertension has been reported in patients with diastolic heart failure, its prevalence and severity remain poorly defined.

Idiopathic pulmonary arterial hypertension (IPAH) has been characterized as a disease of children and young adults,[3,4] yet increasingly the diagnosis is made in elderly persons.[5,6] This raises concern that some patients with dyspnea, unexplained pulmonary hypertension, and a normal ejection fraction could have diastolic heart failure with secondary pulmonary hypertension related to chronic pulmonary venous hypertension. However, as reviewed below, chronic right ventricular pressure overload can cause left ventricular diastolic dysfunction. Thus, a diagnostic dilemma arises in elderly dyspneic patients with otherwise unexplained pulmonary hypertension and a normal ejection fraction or when patients with a presumptive diagnosis of IPAH undergo right heart catheterization and are found to have an elevated pulmonary capillary wedge pressure (PCWP). Do these patients have diastolic heart failure with secondary pulmonary hypertension or is it IPAH causing left ventricular diastolic dysfunction and elevated PCWP?

In this review, illustrative cases of both scenarios outlined above are presented, followed by a discussion of diastolic heart failure, novel concepts relevant to diastolic dysfunction and secondary pulmonary hypertension, and the phenomenon of left ventricular diastolic dysfunction related to chronic right ventricular pressure overload. Lastly, potential diagnostic strategies and implications for therapy are discussed.

CASE 1: A 79-year-old woman presented with acutely decompensated heart failure after starting bosentan for pulmonary hypertension. She had a history of paroxysmal atrial fibrillation that began in 1986 and underwent a surgical MAZE procedure in 1996 because of worsening tachypalpitations. Atrial fibrillation recurred and an atrioventricular node ablation with pacemaker implantation was performed later that year. In 1998 the patient developed symptoms of dyspnea and peripheral edema and was found to have pulmonary vascular congestion on chest radiography. Echocardiography revealed Doppler evidence of severe diastolic dysfunction, no mitral regurgitation and a normal ejection fraction. A diagnosis of diastolic heart failure was made and she was treated with diuretics. In 2000 she had worsening dyspnea and peripheral edema and a repeat echocardiogram demonstrated a normal ejection fraction, severe diastolic dysfunction, and a right ventricular systolic pressure of 56 mmHg. The following year, her condition once again clinically deteriorated. Repeat echocardiography was unchanged with the exception of the right ventricular systolic pressure, which had increased to 75 mmHg. She then underwent a work-up for other secondary causes of pulmonary hypertension, but none were identified and she was referred to the pulmonary hypertension clinic. A right heart catheterization was performed that revealed a pulmonary artery pressure of 73/25 mmHg and a PCWP of 26 mmHg (**Figure 1**) with very prominent V waves in the PCWP wave form. Treatment was started with bosentan, an endothelin receptor antagonist, but she experienced a rapid increase in edema and dyspnea and had pulmonary edema on examination and chest radiography.

The question arises whether or not this patient had late-onset IPAH with concomitant or secondary diastolic dysfunction or diastolic heart failure with secondary pulmonary hypertension. Atrial fibrillation is extremely common among patients with diastolic dysfunction[7] and more common among patients with left heart disease than right heart disease. Demographic, clinical, and echocardiographic information seemed to favor a diagnosis of longstanding diastolic heart failure and would suggest that her pulmonary hypertension is likely related to "reactive" pulmonary hypertension and/or congestive pulmonary vasculopathy as addressed below. However, she was treated with bosentan on the basis of her worsening pulmonary hypertension. In the absence of significant mitral regurgitation, the presence of a large V wave indicates poor atrial compliance, and as outlined below, reduction in atrial compliance may be an impor-

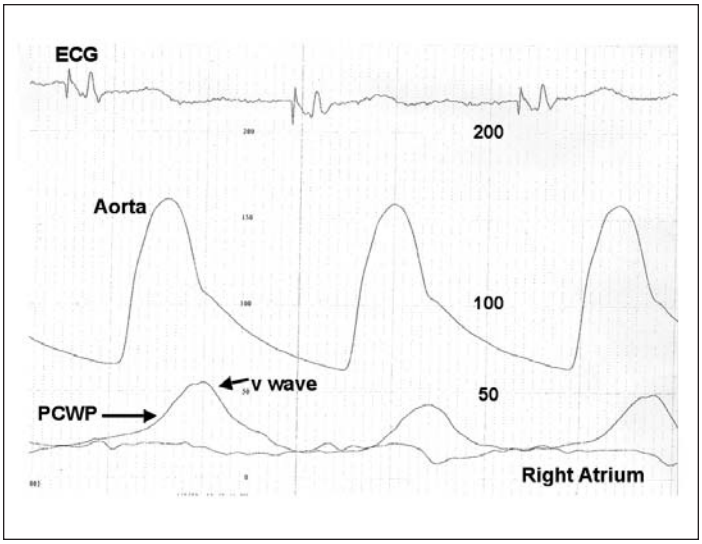

Figure 1. Case 1. Hemodynamic catheterization in an elderly woman with dyspnea and pulmonary hypertension. Electrocardiographic (ECG), aortic, pulmonary capillary wedge pressure (PCWP), and right atrial pressure tracings showing elevated PCWP and a large (50 mmHg) V wave during systole in the PCWP tracing.

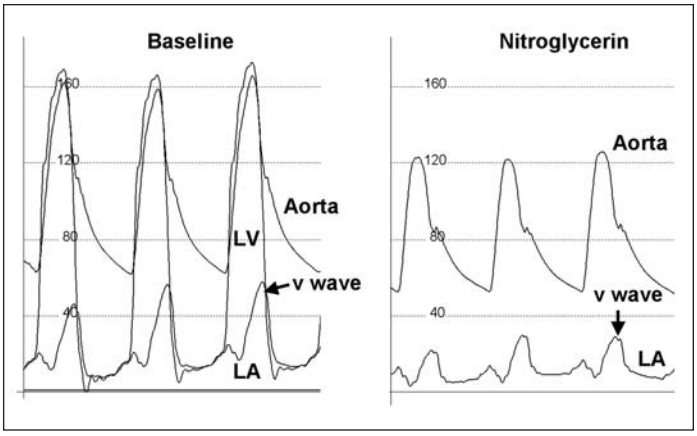

Figure 2. Case 2. Hemodynamic catheterization in an elderly man with dyspnea and pulmonary hypertension. At baseline, aortic, left ventricular (LV), and left atrial (LA) pressures (transseptal approach) were measured. The patient was hypertensive with elevated mean LA pressures where the V wave exceeded 50 mmHg. Nitroglycerin reduced the systemic pressure to 121/51 mmHg. With that the mean LA pressure fell to 15 mmHg and the V wave dropped to 22 mmHg.

tant mediator of secondary pulmonary hypertension in mitral stenosis or in patients with heart failure regardless of ejection fraction. Indeed, large atrial V waves in the absence of mitral regurgitation can occur in patients with several types of cardiac disease.[8,9] This case also underscores the potential for development of worsening pulmonary edema after the initiation of pulmonary vasodilators. This may be related to the preferential vasodilatory effect on the pulmonary vasculature with increased blood flow to a noncompliant left ventricle as has been described with inhaled nitric oxide.[10-13] Alternatively, this may be related to volume retention associated with endothelin receptor antagonism.[14]

CASE 2: A 72-year-old man with a history of long-standing hypertension, atrial fibrillation, diabetes mellitus, and previous aortic valve replacement for aortic stenosis and mitral valve repair for mitral regurgitation presents with progressive dyspnea. Echocardiography demonstrated a normal ejection fraction, a normally functioning aortic prosthesis, diastolic dysfunction, and biatrial enlargement. There was no mitral stenosis and only mild mitral regurgitation. The right ventricular systolic pressure was estimated at 51 mmHg. A right and left heart catheterization using a transseptal approach was performed and revealed systemic arterial hypertension with a central aortic pressure of 170/63 mmHg. Contrast ventriculography revealed only mild mitral regurgitation despite the systemic hypertension. Transseptal left atrial and left ventricular pressures revealed the absence of any significant transmitral gradient. Left atrial pressure tracings demonstrated a large V wave of over 50 mmHg with a mean left atrial pressure of 28 mmHg (**Figure 2**). The pulmonary arterial systolic pressure was 48 mmHg. Nitroglycerin administration reduced the systemic pressure to 121/51 mmHg and the V wave in the left atrium fell to 22 mmHg with a mean left atrial pressure of 15 mmHg.

The hemodynamic profile of this patient is one of diastolic heart failure related to hypertensive heart disease with moderate secondary pulmonary hypertension that was largely due to the passive effects of pulmonary venous hypertension and still reversible with normalization of the PCWP. Again, the presence of large atrial V waves suggests decreased atrial compliance.

CASE 3: An otherwise healthy 30-year-old woman presents with a 12-month history of progressive dyspnea, fatigue, and peripheral edema. Physical examination revealed a markedly elevated jugular venous pressure, loud S_2P, parasternal lift, and peripheral edema. Echocardiography showed normal left ventricular size and function, systolic flattening of the interventricular septum (D-shaped left ventricle), severe right ventricular and right atrial enlargement, a small pericardial effusion (**Figure 3**), mild tricuspid regurgitation, and severe pulmonary hypertension. The estimated right ventricular systolic pressure calculated from the tricuspid regurgitant velocity was 97 mmHg (107% of systemic systolic blood pressure). Left ventricular diastolic assessment with transmitral inflow pulsed-wave Doppler revealed a reduced early-to-late (E/A) filling velocity ratio and a prolonged deceleration time (**Figure 4A**), reduced pulmonary venous diastolic flow velocity (**Figure 4B**), and reduced tissue Doppler early diastolic septal annulus velocity (**Figure 4C**), all suggesting the presence of impaired left ventricular relaxation (grade I diastolic dysfunction). Right heart catheterization confirmed severe pulmonary hypertension and elevated right ventricular diastolic and right atrial pressures in the presence of a normal PCWP.

Although this patient has diastolic dysfunction (impaired relaxation) related to her chronic right ventricular pressure overload, it is not the type of diastolic dysfunction that will be associated with increased filling pressures, at least at rest (see discussion of echo assessment of diastolic function and **Figure 5** below). No formal assessment of left ventricular compliance was performed. However, even if reduced compliance was present, it was not associated with elevated filling pressures in this case. However, her transtricuspid inflow pattern showed a high E/A ratio and a short deceleration time (**Figure 4D**) and her hepatic vein Doppler flow pattern showed reduced systolic for-

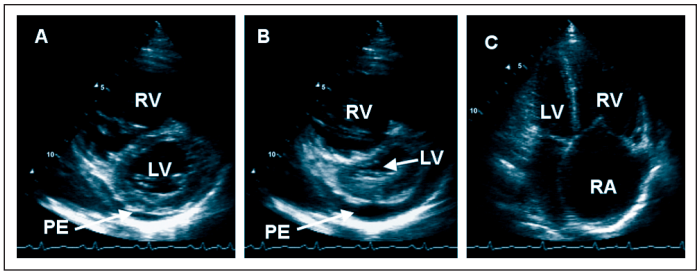

Figure 3. Case 3. Doppler echocardiographic findings in a young woman with severe idiopathic pulmonary arterial hypertension. A. Short-axis view of the right (RV) and left (LV) ventricles in diastole at the mid-LV level. The RV is markedly enlarged while the LV is normal in size. There is a small pericardial effusion (PE). B. Short-axis view of the RV and LV in systole. The intraventricular septum is flattened, producing a D-shaped LV. The PE is more apparent in systole. C. Apical four-chamber view demonstrating the marked RV and right atrial (RA) enlargement.

ward flow and increased atrial reversal velocities (**Figure 4E**); all suggestive of severe right ventricular diastolic dysfunction with reduced right ventricular compliance (grade III-IV diastolic dysfunction). This is consistent with the elevated right atrial pressure demonstrated at her catheterization.

The echocardiogram from this patient illustrates the effect of severe right ventricular pressure overload on right and left ventricular diastolic function. There is evidence of impaired relaxation but no Doppler evidence of decreased left ventricular compliance or elevated filling pressures. This is the type of diastolic dysfunction most frequently observed in patients with IPAH. The concept of ventricular interdependence and its effect on left ventricular diastolic function is discussed in detail below.

Diastolic Heart Failure

Epidemiologic studies have established that 50% of patients with a clinical diagnosis of heart failure have preserved ejection fraction and this entity has been referred to as diastolic heart failure.[1,2] Patients with diastolic heart failure are generally elderly but a significant subset are somewhat younger. Although there is a predominance among women, the syndrome also frequently affects men. More recently, the term "heart failure with normal ejection fraction" has been suggested because of concerns that diastolic dysfunction may not be present in all patients.[15,16]

Risk factors for diastolic heart failure beyond advanced age and female sex include hypertension, coronary artery disease, and risk factors for coronary artery disease, including diabetes.[1] Although classically described in patients with left ventricular hypertrophy, echocardiographic evidence of left ventricular hypertrophy is not uniformly present. Indeed, fewer than 50% of patients have left ventricular hypertrophy in several series of patients with diastolic heart failure.[17,18]

Although the diagnosis of diastolic heart failure is predicated on the presence of clinical heart failure, a normal ejection fraction, and the absence of significant left-sided valve disease, the proper methods to confirm the presence of diastolic dysfunction remain controversial. To characterize left ventricular diastolic function, invasive assessment of the two primary components of diastolic function, left ventricular relaxation and compliance, is needed.

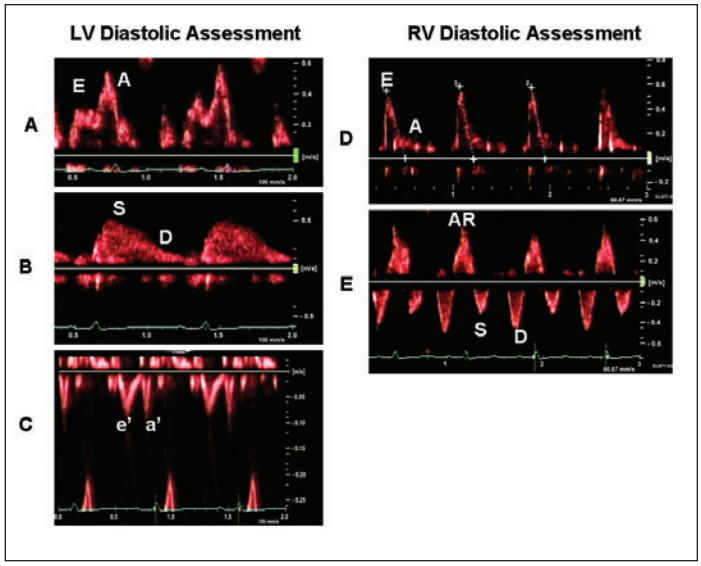

Figure 4. Case 3. Diastolic assessment of the left (LV) and right ventricle (RV) using Doppler echocardiography in the young woman with severe idiopathic pulmonary arterial hypertension shown in Figure 3. LV diastolic assessment (left panels): A. Transmitral pulsed-wave Doppler flow velocity profile. The early diastolic velocity (E) is reduced and the late diastolic velocity (A) is increased. The deceleration time of the E velocity is also increased. B. The pulmonary venous inflow velocity profiles show reduced diastolic forward flow (D) with most flow occurring during ventricular systole (S). C. The mitral annular tissue Doppler profile measured at the septal aspect of the mitral annulus. The early diastolic velocity (e') is low (0.08 m/sec) for a young woman where the e' velocity usually exceeds 0.10 m/sec and usually exceeds the late diastolic velocity (a'). The patterns in A-C are consistent with impaired relaxation in the LV (grade I diastolic dysfunction; see Figure 5). In contrast, diastolic assessment of the RV (right panels) shows that the transtricuspid early diastolic velocity (E) is increased with a shortened deceleration time and there is very little filling in late diastole (A) (panel D). Doppler evaluation of the hepatic veins (E) shows blunted systolic forward flow (S) and marked increase in atrial reversal flow (AR). These findings are consistent with reduced RV compliance and would indicate grade III or IV RV diastolic dysfunction (see Figure 5 for complementary LV pattern).

The degree of impairment in left ventricular relaxation can be quantified by calculating the time constant of isovolumic relaxation (tau) from a high fidelity left ventricular pressure tracing. Impairment in relaxation likely contributes to symptoms of dyspnea with exercise where brisk relaxation is needed to enhance early diastolic filling without increased left atrial pressures. Patients with significantly impaired relaxation are dependent on left ventricular filling during atrial contraction (atrial kick) to maintain filling without increased atrial pressure and thus are prone to develop acute diastolic heart failure associated with the onset of atrial fibrillation. As the speed and extent of left ventricular relaxation are very dependent on afterload, relaxation may become severely impaired with hypertensive episodes[19] and contribute to elevation in mean left atrial pressures, as is likely the case in patients with a normal ejection fraction (hypertensive pulmonary edema).[20]

Assessment of alterations in left ventricular compliance depends on demonstration of an upward and leftward shift of the end diastolic pressure volume relationship (LV-EDPVR) such that the left atrial pressure required to fill the left ventricle to a normal volume is markedly elevated. Marked reduction in left

ventricular compliance is clearly present in patients with rare diseases such as infiltrative cardiomyopathy due to amyloidosis, in those with primary restrictive cardiomyopathies, and in some patients with hypertrophic cardiomyopathy. In these patients, blood pressure is low, left ventricular volumes are normal to reduced, and left atrial pressures are chronically elevated. Attempts to lower atrial pressures with diuretic therapy often result in hypotension as left ventricular filling is dependent on markedly elevated filling pressures. Whether the more typical patients with diastolic heart failure (who are often hypertensive) have reduced left ventricular compliance remains somewhat controversial.[21] Demonstration of reduced compliance mandates the need for the instantaneous assessment of left ventricular pressure and volume over a range of pressures and volumes produced by increasing or decreasing preload. Highly accurate instantaneous assessment of left ventricular volume and pressure is very difficult to obtain. In humans, use of the conductance catheter is really the only means of reliably obtaining such data; although some studies have used echocardiography and left ventricular pressure tracings. Further, even once armed with the data defining the LV-EDPVR, the curvilinear nature of the relationship, which is rarely perfectly monoexponential, makes it difficult to derive a single parameter that reflects the steepness and position of the relationship, and advanced analyses are needed.[22]

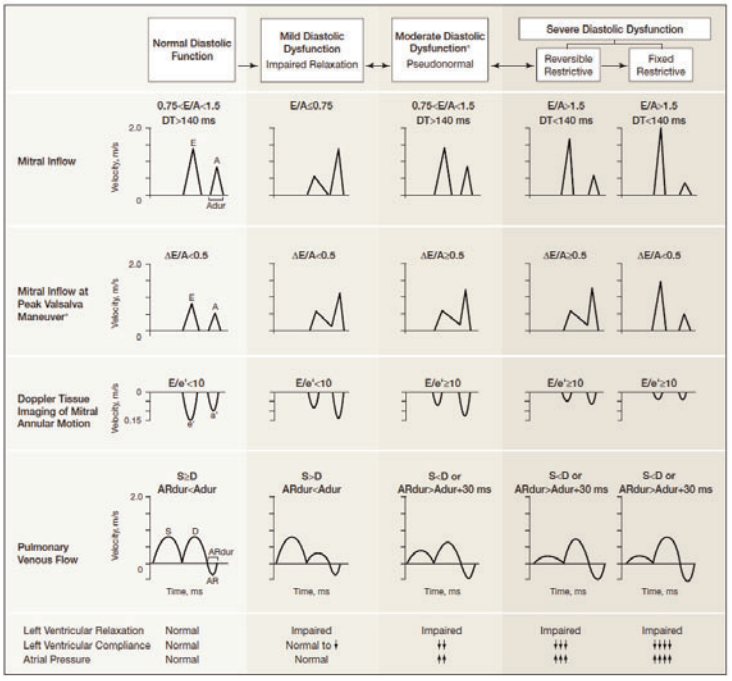

Figure 5. Doppler echocardiographic assessment of diastolic function. E, peak early filling velocity; A, velocity at atrial contraction; DT, deceleration time; Adur, A duration; ARdur, AR duration; S, systolic forward flow; D, diastolic forward flow; AR, pulmonary venous atrial reversal flow; e', velocity of mitral annulus early diastolic motion; a', velocity of mitral annulus motion with atrial systole; DT, mitral E velocity deceleration time. From Redfield et al.[25]

Comprehensive Doppler echocardiography can be very useful in gaining information regarding diastolic function and filling pressures. Doppler patterns (**Figure 5**) consistent with impaired relaxation with normal filling pressure (grade I diastolic dysfunction), impaired relaxation with moderate elevation of filling pressures (grade II diastolic dysfunction), impaired relaxation with severe elevation of filling pressures that can be reversed with preload-reducing maneuvers (grade III diastolic dysfunction), or impaired relaxation with severe elevation of filling pressures that can not be reversed with preload reducing maneuvers (grade IV diastolic dysfunction) have been described and validated against invasive assessment of left ventricular relaxation and filling pressures.[23-25] Equating these Doppler patterns with the severity of diastolic dysfunction makes several assumptions and paramount among these is that the elevation of filling pressures detected by these parameters is mediated by a reduction of left ventricular compliance. Supportive of this assumption is the fact that this grading system has been shown to correlate with worsening prognosis, suggesting that the elevated filling pressures reflected in the Doppler measurements are the result of progressive ventricular remodeling and diastolic dysfunction rather than transient volume overload. Unfortunately, this may not be the case in every patient. Further, diastolic assessment is somewhat difficult to perform, requires informed interpretation, and is limited by atrial fibrillation, tachycardia, conduction defects, and atrial systolic dysfunction. Left atrial enlargement may also be a good indicator of chronic atrial pressure overload and complements the Doppler assessment. Unfortunately, no other noninvasive assessment of diastolic function exists.

Although less frequently performed in clinical practice, similar Doppler interrogation of the tricuspid inflow and hepatic vein inflow can be performed to gain insight into right ventricular diastolic function, as illustrated in Case 3.

Given the difficulty in accurately characterizing diastolic function underscored above, few studies have assessed diastolic function in patients with diastolic heart failure. Invasive assessment of impaired ventricular relaxation and reduced ventricular compliance has been demonstrated in a landmark study of patients with heart failure and normal ejection fraction.[17] Another small but elegant invasive study did not demonstrate a significant alteration in either relaxation or compliance as compared to elderly hypertensive patients without heart failure despite the presence of elevated left ventricular diastolic pressures in heart failure patients.[19] However, in these patients blood pressure and left ventricular diastolic pressure increased dramatically in association with marked impairment in relaxation with exercise. In such patients, arterial stiffening, which promotes labile hypertension and load-dependent diastolic dysfunction, may be an important mechanism contributing to diastolic heart failure even if resting diastolic function is not markedly aberrant. Another study that did not characterize diastolic function invasively but used Doppler assessment of left ventricular filling pressures and 3-D echocardiography to assess volume suggested that volume expansion with normal systolic and diastolic function may produce the clinical syndrome in some patients.[21] It is quite likely that heart failure with normal ejection fraction is a heterogeneous condition with multiple mechanisms contributing to chronic pulmonary venous hypertension.[18]

Diastolic Dysfunction Causing Pulmonary Hypertension

That left-sided heart failure is the most common cause of pulmonary hypertension has long been recognized.[26] The passive effect of pulmonary venous hypertension elevates pulmonary artery pressure. However, patients also develop "reactive" pulmonary hypertension with increases in the transpulmonary gradient. This component of pulmonary hypertension may be related to humoral factors and endothelial dysfunction in chronic heart failure associated with severe systolic dysfunction or mitral stenosis.[27] Finally, chronic pulmonary venous hypertension may lead to congestive pulmonary vasculopathy characterized by pulmonary arteriolar remodeling with medial hyperplasia and intimal fibrosis.[28] Pulmonary hypertension related to reactive pulmonary hypertension and/or congestive pulmonary vasculopathy result in pulmonary hypertension beyond that associated with the passive effects of pulmonary venous hypertension and may not be reversible with acute reduction in pulmonary venous pressures or acute pulmonary vasodilator infusion. Similarly, if medications have normalized resting PCWP or if PCWP primarily becomes elevated with exertion or when blood pressure fluctuates, it may be possible for patients with diastolic heart failure to have elevated pulmonary arterial pressures but a normal PCWP at rest at catheterization and provocative measures may be needed to demonstrate the pulmonary venous hypertension.

Although common in patients with left heart disease, the development of pulmonary hypertension is highly variable. The factors that predispose to development of significant pulmonary hypertension in the presence of chronic pulmonary venous hypertension are not fully understood. As noted above, the presence of humoral activation and endothelial dysfunction likely play a role. Although early case reports described severe pulmonary hypertension in patients with diastolic heart failure, the frequency with which patients with diastolic heart failure develop pulmonary hypertension and its severity remain poorly defined.[29,30] Klapholz et al described the presence of pulmonary hypertension in patients with diastolic heart failure in a larger series of patients with diastolic heart failure and found that the average right ventricular systolic pressure in patients hospitalized with diastolic heart failure was 47 mmHg using Doppler echocardiography.[31] In patients with aortic stenosis, most of whom had a normal ejection fraction, the severity of diastolic dysfunction rather than the severity of aortic stenosis correlated best with the severity of pulmonary hypertension and a significant number of patients developed severe pulmonary hypertension.[32] Similarly, in patients with heart failure and a reduced ejection fraction (systolic heart failure), it was the severity of concomitant diastolic dysfunction rather than ejection fraction or cardiac output that correlated best with the severity of pulmonary hypertension.[33] Thus, diastolic dysfunction associated with valvular disease, reduced ejection fraction, or in isolation is the common mediator that results in chronic pulmonary venous hypertension and secondary pulmonary hypertension. It is therefore not unexpected that patients with diastolic heart failure will develop pulmonary hypertension.

It seems reasonable to expect that elderly persons would be more susceptible to the development of pulmonary hypertension as age related systemic vascular stiffening has been consistently reported[34-37] and age-related pulmonary artery stiffening may well occur. Interestingly, age-related increases in arterial stiffening are worse in women than in men.[34,37-40] Thus, the elderly women patients who develop diastolic heart failure may also be more prone to developing pulmonary hypertension in response to chronic pulmonary venous hypertension associated with diastolic heart failure. Alternatively, some patients may have a primary pulmonary arteriopathy of late onset and have concomitant (but unrelated) diastolic dysfunction related to their age.

Atrial compliance is a little studied factor that may contribute to the pathophysiology of diastolic heart failure and predispose to pulmonary hypertension as well. Insight into the role of atrial compliance comes from early hemodynamic studies where large left atrial V waves were described in patients with various cardiac diseases in the absence of mitral regurgitation.[8,9] The large V wave represents large increases in left atrial pressure in response to the atrial filling that occurs during ventricular systole (closed mitral valve), and thus reflects reduced atrial compliance. Although much focus is placed on left ventricular diastolic pressures in mediating chronic pulmonary venous hypertension, it is *mean* left atrial pressure that reflects the degree of pulmonary vascular congestion[41] and high left atrial pressure during ventricular systole contributes to elevated mean left atrial pressure. Indeed, in patients with mitral stenosis, two recent studies demonstrate that in the absence of mitral regurgitation, the presence of reduced atrial compliance as reflected by large atrial V waves was a potent independent predictor of the severity of pulmonary hypertension in mitral stenosis.[42,43]

Left Ventricular Diastolic Dysfunction in Chronic Right Ventricular Pressure Overload

Chronic right ventricular pressure overload can affect left ventricular diastolic function in several ways. Changes in left ventricular relaxation as well as in compliance (characterized by the LV-EDPVR) have been described.

Left ventricular relaxation is under the triple control of load, myocardial properties, and the uniformity of load in space and time.[44] In chronic right ventricular pressure overload, the load on the intraventricular septum is dramatically increased and as it hypertrophies, the myocardial properties of the septum are altered. The motion of the intraventricular septum in systole and diastole is asynchronous. All these factors could contribute to impairment in global left ventricular relaxation. In Doppler echocardiographic studies of IPAH, impaired relaxation with decreased E/A ratio and increased isovolumic relaxation time and deceleration time have been consistently reported.[45-50] An "impaired relaxation" pattern (grade I diastolic dysfunction) is usually associated with normal left ventricular filling pressures and indeed, patients with severe IPAH entered into clinical trials must have normal PCWP. Thus, based on Doppler echocardiographic studies, the effect of chronic right ventricular pressure overload on relaxation appears unassociated with increases in left ventricular filling pressure.

While patients must have normal PCWP to be diagnosed with IPAH, there is considerable evidence that chronic right ventricular pressure overload can cause reduced left ventricular compliance. The external forces affecting the LV-EDPVR

include right ventricular pressure and pericardial pressure.[51,52] The effect of right ventricular pressures on the LV-EDPVR is termed "ventricular interdependence" and is accentuated in the presence of an intact pericardium. Visner et al. used both acute and chronic canine pulmonary banding models and showed that the LV-EDPVR was shifted leftward (decreased compliance) by acute or chronic right ventricular pressure overload.[53,54] The shift in the LV-EDPVR with acute right ventricular pressure overload was related to ventricular interdependence with decreases in left ventricular volume related to leftward shift of the intraventricular septum as right ventricular pressures increased. These effects were also apparent in chronic right ventricular pressure overload, but a decrease in myocardial compliance (as assessed by the stress-strain relationship) was also seen. This effect, not seen in acute right ventricular pressure overload, suggests that chronic right ventricular pressure overload alters intrinsic left ventricular myocardial properties. Whether this effect is wholly mediated by the altered intraventricular system or whether the left ventricular free wall myocardium also becomes abnormal is unclear. However, Little et al showed that the effect of right ventricular pressures on the LV-EDPVR was attenuated in the presence of chronic right ventricular pressure overload produced by pulmonary artery banding in the dog.[52] Consistent with concepts introduced by Sunagawa et al, Little's study showed that when the stiffness of the septum was greater than the stiffness of the left ventricular free wall, right ventricular pressures had less effect on the LV-EDPVR. Although this study was performed in the absence of the pericardium, Blanchard et al showed that the pericardium remodels in chronic right ventricular pressure overload and that pericardiotomy did not alter right or left ventricular filling pressures or cardiac output.[55]

Although these animal studies and limited studies in the human[56,57] confirm adverse effects of right ventricular pressure overload on left ventricular diastolic function, the clinical significance of left ventricular diastolic dysfunction associated with chronic right ventricular pressure overload is difficult to appreciate. In the studies of Little and Visner, dogs with acute and chronic right ventricular pressure overload had left ventricular diastolic pressures that were not different from those of control dogs. Although the compliance of the left ventricle was reduced, it was not reduced enough to result in elevated left ventricular filling pressures. Similarly, in humans with chronic pulmonary hypertension related to thromboembolic disease, indices of left ventricular diastolic compliance were reduced and improved after thrombectomy, but PCWP was normal both before and after surgery.[57] Lastly, patients entered into IPAH trials have severe pulmonary hypertension, often with severe right ventricular remodeling and dysfunction and yet have normal PCWP. These studies would suggest that while left ventricular diastolic function is altered in IPAH, it is not perturbed enough to result in elevated PCWP. However, as most studies describing hemodynamics in IPAH were performed in the context of a drug trial (where patients with elevated PCWP are excluded), the frequency of left ventricular diastolic dysfunction severe enough to result in elevated filling pressures in patients with IPAH may be underrecognized.

Strategies for Diagnosing Diastolic Heart Failure in the Setting of Pulmonary Hypertension

It is likely that diastolic heart failure is an underrecognized cause of pulmonary hypertension and that otherwise unexplained dyspnea and pulmonary hypertension in elderly patients with a normal ejection fraction and normal valves should prompt consideration of diastolic heart failure as well as IPAH. Yet, distinguishing between diastolic heart failure with secondary pulmonary hypertension and IPAH with secondary diastolic dysfunction can be quite challenging.

Echocardiography may be helpful and evidence of left ventricular hypertrophy, left atrial enlargement, and Doppler evidence of advanced diastolic dysfunction (grades II–IV) may favor the diagnosis of diastolic heart failure. However, not all patients with diastolic heart failure have echocardiographic evidence of left ventricular hypertrophy and not all echocardiographic laboratories perform a comprehensive diastolic assessment nor measure left atrial volume.

All patients with significant pulmonary hypertension should undergo right heart catheterization and if the PCWP is elevated ($\geq$15 mmHg), a diagnosis of isolated pulmonary arteriopathy cannot be made even if there is a significant transpulmonary gradient.[58] In patients with an elevated PCWP, one should look for evidence of systemic hypertension and if present, use of a systemic vasodilator to lower arterial pressures should be considered. Prompt reduction in PCWP with normalization of blood pressure supports the diagnosis of diastolic heart failure. Provocative testing with exercise in elderly patients with pulmonary hypertension in whom diastolic heart failure is suspected may be useful. Marked elevation in PCWP and blood pressure with exercise would support the diagnosis of diastolic heart failure that could be causing the patients' symptoms and their pulmonary hypertension. Patients with severe IPAH should not experience increases in PCWP during exercise[59]. Additionally, one should look for evidence of reduced atrial compliance (large V waves in the PCWP tracing). Exercise testing may also be helpful and if associated with marked increases in PCWP, a diagnosis of diastolic heart failure would be supported.[59] Finally, if diastolic heart failure is strongly suspected, care should be taken with use of vasodilators that are very selective for the pulmonary vasculature (such as inhaled nitric oxide) as increases in right heart output in the presence of a noncompliant left ventricle may result in further increases in left atrial pressure and pulmonary edema, as outlined above.[10-13]

Therapeutic Implications

To date, patients with pulmonary hypertension and a PCWP of 15 mmHg or greater have been excluded from pulmonary arterial hypertension drug trials. It remains unclear how often patients with suspected pulmonary arterial hypertension and an elevated PCWP are treated with new therapies and whether they experience benefit. Similarly, whether patients with diastolic heart failure and pulmonary hypertension would benefit from specific treatment of the pulmonary hypertension is unclear. Although use of epoprostenol was associated with increased mortality in patients with systolic heart failure,[60] the mechanism responsible for the increased mortality is unclear and the outcome in diastolic heart failure, or with alternate agents, may be different and deserves consideration.

Back to the Patients

Case 1. This patient demonstrates the progressive development of pulmonary hypertension on a background of longstanding and fairly well documented diastolic heart failure. We would speculate that she has secondary pulmonary hypertension and not IPAH of late onset. While her pulmonary hypertension may be characterized by some as "out of proportion to her left heart disease," without knowledge of severity of her chronic pulmonary venous hypertension, one can not conclude that is the case. Certainly, chronic pulmonary venous hypertension related to mitral stenosis (the ultimate diastolic dysfunction) can result in severe pulmonary hypertension that is accompanied by increased transpulmonary gradient and that can take months to years to resolve after treatment of mitral stenosis.

Treatment for diastolic heart failure is supportive as no therapy has been documented to improve outcomes in this condition. Thus, consideration of specific therapy for pulmonary hypertension in such patients is not unreasonable. As the use of agents for IPAH have been expanded to patients with pulmonary hypertension related to connective tissue disease, expansion to use in patients with diastolic heart failure and secondary pulmonary hypertension would be a reasonable avenue for investigation. However, the potential for worsening pulmonary congestion must be recognized, as was observed in this patient.

Case 2. This patient demonstrates a milder form of pulmonary hypertension secondary to diastolic heart failure. In this case, the pulmonary hypertension is largely related to the passive effect of the pulmonary venous hypertension and is acutely reversible. The diagnosis of diastolic heart failure with secondary pulmonary hypertension is much easier to make in this instance.

Case 3. This patient has IPAH and has diastolic dysfunction but does not have elevated PCWP. The impairment in left ventricular relaxation mediated by the abnormal septum and septal motion causes characteristic changes in the left ventricular diastolic parameters that are generally associated with normal filling pressures at rest. Although decreases in left ventricular compliance related to ventricular interdependence have been described in animal models, and could lead to elevated left ventricular filling pressures, elevated left ventricular filling pressures are not commonly seen in patients with IPAH. However, as formal assessment of left ventricular compliance with pressure volume analysis over a range of preloads was not performed in this patient, we can not exclude the presence of decreased compliance with normal PCWP related to decreased filling as a result of her severe pulmonary hypertension and right ventricular dysfunction. In contrast, she has severe right ventricular systolic and diastolic dysfunction with elevated right ventricular diastolic pressure. ■

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