Pulmonary Hypertension: A Common Complication of Left Heart Disease

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Pulmonary hypertension (PH) commonly results as a complication of left heart failure (systolic or nonsystolic dysfunction). It is important to note that there is a distinct difference between PH as a whole and pulmonary arterial hypertension (PAH), which have the same criteria with regard to mean pulmonary artery pressure (mPAP) as PAH with the critical difference of the pulmonary capillary wedge pressure (PCWP) measurement. Table 1 shows the most common causes of RV dysfunction. The issue of management of right ventricular (RV) failure has recently become more important with increased awareness of RV failure symptoms in the setting of PH. Moreover, with growing consideration for surgical left ventricular support (left ventricular assist device, LVAD) and the need for RV functional competence, the need to better understand the role of RV function is becoming more paramount.

PATHOPHYSIOLOGY

Heart failure has 2 components: diastolic and systolic failure. Diastolic heart failure involves high left ventricular (LV) filling pressures in the setting of a normal ejection fraction (HFpEF), while systolic heart failure involves elevated LV filling pressures in the setting of a reduced LV output. Regardless of the cause of heart failure, the increased LV filling pressure results in consequential elevated pressures in the left atrium and pulmonary venous vasculature owing to the closed nature of the hemodynamic system. This elevated filling pressure is seen in the PCWP measurements at the time of the right heart catheterization and the LV end diastolic pressure (LVEDP) if measured directly. The pulmonary vascular impact of the elevated venous pressures can manifest in 2 distinct states: reactive PH or fixed PH.

Reactive PH is an elevated PAP in the setting of elevated LV filling pressures in which reduction of the LV filling pressures results in resolution of PH. Thus, the elevation in PAP is due to the elevated left-sided filling pressures, related to either systolic or diastolic dysfunction, and resolves rapidly with volume removal. This appears to be the more common type of PH related to LV disease.[1] It has been reported that in many cases, pharmacologic (diuretic) or mechanical (LVAD implantation) reduction in PCWP results in a relatively rapid resolution of PH. In this regard, aggressive management of volume and other risk factors that promote pulmonary venous hypertension and heart failure (sleep apnea, diabetes, systemic hypertension, hypercholesterolemia) is warranted in an effort to prevent potential conversion of the reactive PH to a more sustained type of PH. While this has been mostly attributed to those patients with systolic LV dysfunction (LVD), the same can be true with patients with diastolic heart failure (HFpEF).[1]

Fixed PH from LVD is becoming more readily acknowledged as a disease entity. As elevated LV filling pressures become more chronic, it is possible that the pulmonary vasculature remodels in such a way as to protect itself from pulmonary edema. This remodeling of the precapillary and postcapillary pulmonary vasculature results in PH that is not fully responsive to a decrease in LV filling pressures. Often, in the setting of normalized volume, this type of PH is called "out of proportion" to the underlying left-sided heart disease. The pathology of this fixed PH is similar to that sometimes observed in conditions of mitral valve regurgitation or mitral valve stenosis. In the case of valvular disease, the PH often persists after valve repair or replacement.[1-4] It is not clear if there is a time course of resolution of PH in this setting.

Under chronic conditions, the RV can adapt to an increase in ventricular afterload either by an increase in myocardial contractility or by an increase in preload.[4] This is true for a normal right ventricle. Chronic pressure overload on the RV results in RV hypertrophy with changes in the functional anatomy. The normal peristaltic contraction, which consists of contraction of the papillary muscles followed by movement of RV free wall and finally LV wringing that helps emptying of RV, is lost in chronic volume overload.[5] This causes an accelerated increase of PAP and flow.[6] The change in contraction and ejection limits the inotropic adaptation of the RV with chronic volume overload.[5]

Regardless of the source of the increase in afterload, the RV hypertrophies in an effort to compensate for the increased load. This hypertrophic response is generally regarded as a salutary response. However, with a prolonged increase in load, systolic function starts to decline, as hypertrophic response may be inadequate to compensate for systolic stress.[1,5] This decline in RV function later results in clinical signs/symptoms of heart failure. Furthermore, any valvular disease such as tricuspid or pulmonic regurgitation thwarts the Frank-Starling compensatory mechanism. Thus, volume and pressure overload often coexist in the etiology of heart failure.[1] It is currently unclear as to whether there really is a "transformation" from physiologic hypertrophy into pathologic hypertrophy with subsequent heart failure.[5]

CLINICAL EVALUATION

Signs and Symptoms

The clinical picture of PH associated with left heart disease usually depends on the overall volume status of the patient and

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Table 1: Common Causes of RV Dysfunction

I. Volume overload
• Tricuspid regurgitation
• Pulmonic regurgitation
• Atrial septal defect
• Anomalous pulmonary venous return
II. Pressure overload
• LV failure
1. Systolic dysfunction resulting in pulmonary venous hypertension
2. Diastolic dysfunction resulting in pulmonary venous hypertension
• Cor-pulmonale
1. Pulmonary hypertension
2. Pulmonary emboli
3. COPD
• Mitral valve disease
• Ventricular septal defect
• Pulmonic stenosis
• Atrial myxoma
• Abnormal aortopulmonary communication
III. RV myocardial dysfunction
• RV infarction
• RV dysplasia
• Dilated cardiomyopathy
IV. RV inflow impedance
• Pericardial disease
• Restrictive cardiomyopathy
• Cardiac tamponade
• Tricuspid stenosis

the presence or absence of elevated filling pressures and depressed cardiac output. Patients with PH often complain of an insidious onset of fatigue, lethargy, and dyspnea. Regardless of the cause of right heart failure, symptoms of dyspnea, exertional syncope, and palpitations often suggest decreased cardiac output, while lower extremity edema and ascites imply increased preload and right heart failure. The presence of orthopnea and paroxysms of nocturnal dyspnea is usually absent in isolated PAH, and should raise the suspicion for elevated left heart filling pressures. Moreover, elevated LV filling pressures may also prompt increased nighttime cough and supine chest discomfort. While exertional chest discomfort may prompt concern for ischemic heart disease, it may also occur in the setting of elevated LV filling pressure.

Physical Examination

The physical examination may reveal a RV heave or right-sided gallop (S4) with or without elevated jugular venous pressure, ascites, peripheral edema, or evidence of poor systemic perfusion with cool extremities and decreased pulse volume.[1] Again, clues to etiology can be found by the presence of crackles that may suggest either parenchymal lung disease or elevated left heart filling pressures. In advanced right heart failure, cardiogenic shock ensues, which may be difficult to differentiate at the bedside from advanced left heart failure.

DIAGNOSTIC EVALUATION

Diagnostic evaluations are performed to confirm the presence and etiology of PH. While chest radiography, either computed tomogram (CT) or plain radiograph, may show right heart size in addition to visualization of the pulmonary arteries, neither allows functional assessment of the RV or LV. Echocardiography and, more recently, cardiac CT and magnetic resonance imaging (MRI) have been used to confirm the clinical suspicion of RV/LV dysfunction. Both imaging modalities are noninvasive; however, they each have unique features that may make them more suitable for particular clinical presentations. These aspects of the diagnostic evaluation for PH using echocardiography and right heart catheterizations are described in other sections. MRI and magnetic resonance angiography (MRA) are techniques that can, noninvasively and in a single setting, provide multiple data ranging from structure (RV volume, mass, pulmonary angiography) to function (RV function, pulmonary blood flow/perfusion) to molecular imaging. All of the described studies can be performed in standard clinical 1.5T magnets and can be completed with or without small amount of gadolinium contrast injected through a peripheral vein. More importantly, they could be completed within a relatively short period of time (ie, less than one hour), providing a comprehensive assessment with a single test. There have been major advances in MRI techniques in the last several years with ECG gating and respiratory suppression, diminishing imaging artifacts and allowing for computations of RV volumes. The complex 3D structure of the RV can be directly studied with MRI in order to measure RV volume and mass,[6,7] without the need for computational assumptions; values for RV mass and volume in normal cohorts have also been reported.[8] In stacks of contiguous 5-10 mm slices, endocardial and epicardial contours can be drawn in end-systole and end-diastole.[9,10] The sum of the individual slice volumes will give the end-systolic (RVES) and end-diastolic (RVED) volumes respectively, from which RV ejection fraction (RVEF) can be calculated ([RVEDV-RVESV]/RVEDV). RV mass can be calculated by multiplying RV volume with the myocardium specific gravity (1.05 g/cm3). The anatomy of the RV is more complex than the LV and moderator bands can vary in presence and size, and while some can include them in the tracing of the RV endocardial contour, others might not. This results in somewhat lower inter-study reproducibility in the RV when compared to the LV, but this is overall very high and definitely better than echocardiograph,[11,12] making MRI

the gold standard in the study of RV size and function. Moreover, MRI allows for the measurement of eccentricity index with good reproducibility.[13]

RV hypertrophy is mostly an adaptive or compensated state in response to the increased RV afterload. In this regard, RV mass correlates well with PAP.[14,15] Beyond that stage, RV enlargement is associated with decrease in RV contractility, further decreases in cardiac output, worsening right heart failure, and death. Therefore, it is not surprising that in a prospective study of 64 PAH patients followed for 32 months, RV volume at diagnosis was a strong predictor of mortality, stronger than RV mass.[16] Further RV dilatation at follow-up was an even stronger predictor of survival.[16]

MANAGEMENT

Medical Management

Initial management of PH with LV dysfunction. Although PH in LVD is prevalent, the significant clinical data directed at its treatment are lacking. It is important to note that there is no specific FDA-approved therapy for the treatment of PH with LVD. In large part, the initial therapies for the treatment of PH rest in the aggressive management of the underlying condition, heart failure, and the risk factors that worsen the disease (sleep disordered breathing, systemic hypertension, diabetes, obesity, etc). It is equally important to separate the underlying LVD by the underlying cause (systolic dysfunction [reduced ejection fraction] vs diastolic dysfunction [DHF or HFpEF]) as the potential treatment options differ. There is much more information related to those patients with LV systolic dysfunction. As PH in patients with LV failure is often linked to elevated PCWP, most treatments are directed toward normalization of pulmonary wedge pressure.[11] Volume management represents the first line of therapy in the treatment of PH with LVD. In addition, neurohormonal modulation is critical to the treatment of LV systolic dysfunction.[17,18] In this regard, the use of beta-blockade and modulation of the renin-angiotensin axis reduces readmission and improves mortality in those patients with LV systolic dysfunction. This management of heart failure will also assist in management of LV filling pressures and consequently, elevated pulmonary pressures. Angiotensin-converting enzyme (ACE) inhibitors have been shown to attenuate pulmonary pressor response in an animal model of PH.[15] More recently, studies using aldosterone antagonists (EMPHASIS-HF) have further expanded the indication of aldosterone antagonists in the management of heart failure. Once on optimal medical therapy, other considerations should be made in the management of heart failure through the use of cardiac resynchronization therapy (CRT).[17,18]

In addition to proper neurohormonal modulation, aggressive risk reduction should also be practiced in patients with comorbid conditions. The aggressive management of systemic hypertension, diabetes, hyperlipidemia, and sleep disordered breathing is warranted. Hypoxia should also be addressed as it contributes to vasoconstriction. All patients with PH should have peripheral oxygen saturation of 90% or greater or PaO2 >60 mm Hg.[13]

Use of PAH-directed therapy in the treatment of PH secondary to LV systolic dysfunction. Prostacyclin analogs were first studied in patients with LV systolic heart failure. FIRST (Flolan International Randomized Survival Trial) showed an increase in mortality in patients with LV failure treated with long-term epoprostenol. The explanations behind this negative outcome are not clear, though may be related to the positive inotropic effect of epoprostenol.[22] Iloprost, a prostacyclin analog given as inhaled route, has shown beneficial effects in decreasing mPAP and increasing cardiac index (CI) in acute settings. Even though there are no long-term data available in this patient population, especially in patients with LVD, there are several short-term and perioperative studies that support the potential use in this patient population, particularly if/when volume is properly managed.[19-23]

Endothelin receptor antagonists (ERAs) have also been studied in heart failure. Worsening of heart failure was noted in the REACH-I (Research on Endothelin Antagonism in chronic heart failure) study in which patients with an EF <35% were randomized to receive either placebo or 500 mg twice daily dose of bosentan (a nonselective endothelin receptor A and B antagonist [ET_A and ET_B]). This trial was stopped early due to liver dysfunction in treatment arm. But for those patients who completed study protocol of 26 weeks, there was improvement in the New York Heart Association (NYHA) class in the treatment group.[24] Later, the ENABLE (Endothelin Antagonist Bosentan for Lowering cardiac Events in heart failure) study was a phase III evaluation of a lower dose of bosentan in patients with chronic heart failure and ejection fraction of <35%. A total of 1613 patients were randomized to placebo or bosentan at 125 mg twice a day with mean follow-up of 18 months. There was no difference in the primary end point between 2 groups of all-cause mortality or hospitalization. But there was an increase in early worsening of heart failure in the bosentan treatment arm.[24] Neither of these studies targeted patients with PH or measured hemodynamics. Furthermore, these trials involved nonselective antagonism of ET_A or ET_B receptors. It is unknown if selective ET_A antagonism will prove superior to nonselective antagonism. Moreover, these studies did not specifically examine therapy in patients with optimized LV filling pressures, which likely is critical to assessing a pulmonary vascular response.

More recently, phosphodiesterase inhibitors have been studied in the treatment of PH associated with heart failure. Sildenafil, a phosphodiesterase type 5A (PDE5A) inhibitor, increases cGMP mediated relaxation and growth inhibition of the vascular smooth muscle cells including those in the lungs. There are emerging data that it may be useful for PH with left heart failure. In a hemodynamic study of 14 patients with heart failure who were administered 25 mg or 50 mg 3 times daily dosing of sildenafil for 24 hours, marked decrease in mPAP and pulmonary vascular resistance (PVR) were demonstrated.[24] There was greater improvement in patients who received the higher dose,

and it was shown to be safe and well tolerated in this patient population.[24] Moreover, a study of patients with fixed PH in LV disease post-LVAD implantation showed a significant improvement in PVR and RV contractility index with sildenafil treatment for up to 15 weeks, bringing PVR down from an average of 5.5 Wood units to less than 3 Wood units such that transplantation was possible.[4] Again, there are no long-term data available, but the future of sildenafil treatment in PH with LVD appears promising. Moreover, studies examining the effects of sildenafil acutely and with long-term treatment have shown improved exercise tolerance and quality of life in patients with heart failure (see "Clinical Trials" on page 60 of this issue).[25-28]

Surgical Management

Surgical management of advanced heart failure. Cardiac transplantation is the definitive treatment for those patients with advanced heart failure and an option of last resort. However, preoperative PH is a predictor for mortality for patients undergoing heart transplantation. A PVR of greater than 5 Wood units with maximal vasodilatation is considered to be a relative contraindication to cardiac transplant. Patients with unacceptably high PVR are treated with medical management to try and optimize hemodynamics as previously discussed.

Use of intra-aortic balloon counterpulsion may be useful in patients with normal systemic pressures and refractory elevation of pulmonary pressures. This technique is used primarily in the perioperative setting to maintain and improve cardiac output and therefore PVR, reduce afterload, and enhance diastolic coronary filling; however, the role for treatment of pure right heart failure is limited.

Recently, more invasive procedures including ventricular assist devices (VAD) have been used in treatment of advanced heart failure. LVADs can lead to a decrease in left atrial and pulmonary pressures as well as reduction in RV afterload. Biventricular assist device (BiVAD) has been shown to reduce right atrial pressure, mPAP, and PCWP via the concomitant reduction in RV and LV filling pressures. BiVADs resulted in a reduction in RV size as well as restoration of isoproterenol response in isolated muscle strips from the explanted RV.[29,30]

Finally, total artificial heart (TAH), has the ability to provide complete support. TAH requires sufficient intrathoracic space for accommodation. This device is still in phase III clinical trials.[31-33]

CONCLUSION

The development of new therapeutic strategies specifically for PH in LVD should be promoted. These new strategies might include cell-based or gene therapy, new drugs, or new combinations of existing treatments. Awareness should be promoted in the pulmonary and cardiology research communities about the lack of knowledge of the disease with well-publicized requests for research proposals. This will ultimately lead to better treatment and preventive means to reduce morbidity and mortality associated with right heart failure and left heart failure.

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