Pulmonary Hypertension Due to Valvular Heart Disease: Aortic and Mitral

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Pulmonary hypertension (PH) can be due to a primary pulmonary vasculature abnormality, but is more often secondary to lung, cardiac, or environmental insults, and is frequently multifactorial. Most commonly, left heart disease is at fault, a subset of which is valvular heart disease (VHD). With sufficient time, most chronic left-sided valve lesions will result in some element of PH. Long-standing PH causes pulmonary vascular remodeling and progressive PH due to reduced vascular compliance. Careful monitoring of VHD progression is critical, both through screening imaging and patient education, in order to properly time intervention to prevent the development or worsening of PH. The primary diagnostic tool in PH due to VHD is echocardiography, while invasive hemodynamic evaluation can be helpful to determine PH etiology or severity when echocardiography is not adequate. The presence of PH in VHD is often an indication for intervention, but it also increases procedural risk. Severe PH, however, has not been proven to preclude safe intervention, but rather should prompt full preprocedural evaluation and close intra- and postprocedural monitoring. Valve replacement or repair can be viewed as a treatment for PH secondary to the valvular lesion. Percutaneous alternatives to surgical interventions are available for some mitral and aortic valve conditions. Though in relatively early stages of development, these less invasive procedures may improve the safety profile of valve interventions. Pulmonary hypertension that fails to improve after intervention should raise suspicion for procedural failure or underlying pulmonary vascular disease (either precapillary possibly in association with interstitial lung disease or scleroderma or secondary to combined pre-/postcapillary PH due to long-standing pulmonary venous hypertension). This review is focused on the pathophysiology, treatment options, and outcomes in patients with PH due to mitral and aortic valve lesions.

PREVALENCE AND PATHOPHYSIOLOGY

Pulmonary hypertension (PH) due to left-sided heart disease (LHD), classified by the World Health Organization as Group 2 (WHO 2), is secondary to left ventricular (LV) systolic dysfunction (heart failure with reduced ejection fraction – HFrEF), LV diastolic dysfunction (heart failure with preserved ejection fraction – HFpEF), or valvular heart disease (VHD). The principle insult in this class of PH is elevated left ventricular end diastolic pressure (LVEDP, and/or left atrial pressures), which is transmitted to the pulmonary vasculature, raising pulmonary artery pressure (PAP). This PH physiology is postcapillary and defined as a mean PAP (mPAP) ≥25 mm Hg and the pulmonary capillary wedge pressure (PCWP) is >15 mm Hg. Other hemodynamic features of postcapillary PH include increased left atrial pressure (>15 mm Hg) and/or increased LVEDP (>15 mm Hg). When the difference between mPAP and PCWP (known as transpulmonary gradient, TPG) is ≤12 mm Hg, pulmonary diastolic gradient (PDG) <7, and/or the pulmonary vascular resistance (PVR) is <3 Wood units, the elevated PAP is attributable to left heart disease and is considered passive pulmonary venous hypertension. If the TPG is >12 mm Hg or the PVR is ≥3 Wood units, the PH is described as combined precapillary-postcapillary PH (CPpPH). This previously described “postcapillary reactive” or exaggerated PH can have a variety of mechanisms and comorbidities, particularly in the aging population. Most often, this is due to long-standing pulmonary venous hypertension causing significant vascular remodeling and decreased pulmonary circulation compliance. Repetitive and sustained injury to the pulmonary vasculature results in pathologic changes at the cellular level (increased neurohormonal feedback, endothelin-1 and cytokine activation, decreased nitric oxide and brain natriuretic peptide). But complicating the primary insult of pulmonary venous hypertension, other common comorbidities include: lung disease that can be abnormal lung physiology from sleep apnea, aging-related decreased lung function, anemia, atrial fibrillation, and renal failure may all play a role in the combined pre-/postcapillary phenotype.

Key Words—aortic stenosis, congenital heart disease, echocardiography, mitral valve, valvular heart disease
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Disclosures: Dr Kaple has nothing to disclose. Dr Horn has served as a consultant/advisory board/steering committee member for Ikaria, Novartis Pharmaceuticals, and Janssen. She has received institutional grant/research support from Actelion Pharmaceuticals, St. Jude Medical, Gilead Sciences, Ikaria, Sunshine Heart, and CardioKinetics.
WHO 2 PH – HFrEF, an independent risk factor for increased mortality in HFrEF, is an essential part of the evaluation with respect to pulmonary vascular reactivity for heart transplant. In this population, PH may be reversible with appropriate use of a durable left ventricular assist device (LVAD) to improve the left-sided hemodynamics and lead to reversibility over several months. WHO 2 PH in HFrEF may be more complicated given that the disease itself includes different phenotypes. The disease is often multifactorial, with mixed etiologies and needing a multidisciplinary approach to address treatable underlying causes. Pulmonary hypertension in VHD requires careful analysis to choose the right patient for appropriate valvular interventions insomuch as valvular repair/replacement is the treatment of choice for the valvular-related WHO 2 PH. Aortic and mitral valve disease, both insufficiency and stenosis, can lead to the downstream development of PH. The prevalence of PH-VHD is difficult to determine due to varying cutoff values and methods of assessment in the published literature. Furthermore, limitations of echocardiographic and invasive hemodynamic measurements of PAP add further limitations. Echocardiography may over- or underestimate PAP and requires an adequate jet of tricuspid regurgitation (TR), while invasive measurements are often subject to referral bias. Elevated PAP has long been recognized as a complication of mitral stenosis (MS). Hart et al reported 73% of 317 patients with severe MS undergoing percutaneous mitral balloon valvuloplasty (PMBV) had mPAP >25 mm Hg. Roughly two-thirds of patients with severe aortic stenosis have PH. By comparison, the development of PH in mitral regurgitation (MR) is dependent on the valvular abnormality and chronicity. Barbieri et al demonstrated that degenerative MR due to a flail leaflet causes PH at baseline in 23% of patients. The prevalence of PH in functional MR is up to 44%, and is dependent on LV loading conditions as well as left atrial compliance and function. Patients with a greater amount of MR are more likely to have PH, as demonstrated in a cohort study of 1541 patients with HFrEF. This study also demonstrated that patients with a precapillary component to PH or worse LV diastolic dysfunction had more severe MR.

**Assessment**

A new diagnosis of PH should prompt a detailed evaluation of the left heart, including assessment of valvular function. One should obtain a detailed history, focusing on risk factors for LHD (assessment for risk factors, prior congenital heart disease, known cardiac murmurs or valvular heart disease, coronary artery disease) and symptoms (especially effort tolerance, orthopnea, and paroxysmal nocturnal dyspnea). Physical examination findings for right heart failure due to PH are often non-specific (edema, hypotension, elevated jugular venous pressure, loud pulmonic valve closure, right ventricular lift, right-sided S3). Signs of pulmonary edema and an audible S3 or S4 are more specific for LHD. Cardiac auscultation for classic findings of aortic and mitral pathologies should be performed, the specifics of which are beyond the scope of this review. Electrocardiography can be useful to demonstrate chamber enlargement and identify conduction and rhythm abnormalities, though most findings lack sensitivity for valvular pathologies. Chest radiography with an x-ray or computed tomography (CT) will help demonstrate pulmonary edema, chamber enlargement, and potentially valvular calcification.

Echocardiography is the primary diagnostic tool for valvular heart disease, as it is a cost-effective method with high sensitivity and specificity, providing both structural and hemodynamic information. Pulmonary artery systolic pressure (PASP) can be calculated using the modified Bernoulli equation (PASP = 4*(tricuspid regurgitation jet velocity)^2 + right atrial pressure). This method can over- and underestimate PAP, and requires a high-quality Doppler signal from an adequate TR jet, which has been reported to be lacking in up to 89% of ambulatory heart failure patients. Agitated saline contrast can be used to determine the presence of shunts, which are not uncommon in the setting of PH or congenital heart disease. Provided there are adequate acoustic windows, echocardiography allows for accurate assessment of mitral and aortic stenosis and regurgitation (both of native and bioprosthetic valves using M-Mode, 2D and 3D imaging). Standardized and validated definitions for MS, MR, aortic stenosis (AS), and aortic insufficiency (AI) are provided through the American Society of Echocardiography. Echocardiography also allows for evaluation of endocarditis lesions, which can cause significant valvular regurgitation. Mode of failure of bioprosthetic valves can be determined by echo, such as regurgitation (perivalvular or central), valve dehiscence, or stenosis (leaflet immobility, calcification, or patient prosthesis mismatch).

Cardiac magnetic resonance imaging (CMR) is an expensive tool, but can provide accurate assessment of valvular regurgitation (including regurgitant fraction), chamber size and function, jet velocities through stenotic valves, and congenital heart disease. Given that transthoracic echocardiogram (TTE) can underassess severity of MR, in the right patient cohort, use of either CMR or transesophageal echocardiogram (TEE) is often recommended to detect more significant regurgitation.

Invasive right heart catheterization (RHC) with a balloon-directed pulmonary artery catheter is the gold standard for determining PAP. When combined with echocardiographic data, invasive hemodynamics can help differentiate the etiology of PH, which is often multifactorial. Provocative testing (exercise and fluid challenge) and vasodilator testing can be performed as well to help isolate the pre- and postcapillary components of PH and determine the true PH etiology. Data from RHC can also be useful in optimizing medical therapy in PH-VHD. Pressures in each chamber (right atrium, right ventricle, and pulmonary artery) and PCWP should be taken at end expiration in spontaneously breathing patients. Fick cardiac output (CO) or thermodilution CO should be calculated, the latter being the preference in low CO patients. The PCWP tracing in MR demonstrates...
tall V waves, representing the transmitted wave of pressure, which occurs during LV systole. Direct LV pressure measurement should be considered if PCWP is not reliable or yields an unexpected finding. When echocardiography findings are incongruent with clinical findings of MS or AS, one should consider invasive measurement of transvalvular gradients.

**MANAGEMENT**

**General Comments**

Treatment for PH-LHD should begin with guideline-directed pharmacologic treatment for the underlying HFpEF and HFrEF: diuretics, vasodilators, and neurohormonal antagonists. In addition, patients should be considered for mechanical support and resynchronization therapy when appropriate. Targeted therapies for PH-LHD are lacking, showing only limited benefit in symptomatic improvement without affecting clinical survival. However, the subset of PH due to VHD is an exception: surgical and percutaneous interventions for underlying valvular lesions have a meaningful impact on improving PH.

The development of PH is often an indication for mitral valve (MV) or atrioventricular (AV) intervention, but has also been well documented to be a procedural risk factor. Interventions for VHD include surgical approaches, but percutaneous approaches are rapidly being adopted for patients who are high or prohibitive risk for surgery (often elderly patients with multiple comorbidities). The postcapillary component of PH will improve after valve intervention. The degree to which the precapillary component of PH (due to pulmonary vascular remodeling secondary to long-standing PH) can improve after intervention remains unpredictable. Patient prosthesis mismatch after valve replacement (especially after MV replacement) must be considered as a cause of persistently elevated PAP.

**Mitral Stenosis**

Severe MS will result in left atrial hypertension and some degree of PH over time, often in the severe range. Roughly three-fourths of patients will have mPAP >25 mm Hg at the time of PMBV, and one-quarter in the severe range (defined by PVR >6 Wood units). Pulmonary hypertension in the setting of MS appears to be a function of poor atrial compliance (defined as (MV area, MVA)/(mitral E wave downslope) <4 mL/mm Hg), which is in turn a predictor of worse functional capacity and the need for MV replacement or repair. Early concerns for predictable and durable improvement of PH after MV surgery were addressed by Braunwald et al, who reported full pre- and postoperative hemodynamic changes in a cohort of 31 patients. This pivotal trial showed an improvement in PVR (543 to 243 dyne-s-cm⁻⁵) and increased pulmonary blood flow in patients with MV repair for mitral stenosis.

Severity of MS is based on mean gradient, PASP, and valve area (severe range: mean gradient >10 mm Hg, PASP >50 mm Hg, and MV area of <1.0 cm²). Estimated 5-year survival for unrepaired symptomatic MS is 44%. Echocardiographic assessment will demonstrate severity of obstruction, leaflet mobility, thickening, calcification, and subvalvular involvement, all of which are used to calculate the Wilkins score. Symptomatic (New York Heart Association [NYHA] functional class II) patients with a Wilkins score <8 and less than moderate MR can be considered for PMBV. Patients with asymptomatic moderate or severe MS can be considered for PMBV with resting PASP >50 mm Hg, or exercise-induced PASP >60, PCWP >25 mm Hg, or MV gradient >15 mm Hg. Successful PMBV is defined as increasing MVA to 1.5 cm² or ≥50% increase in MVA with <3 MR. Freedom from death, repeat PMBV, or MV replacement is 50% to 65% at 3-7 years (80% to 90% with the most favorable valve morphology).

As shown in Table 1, there are 2 general categories of MR based on the underlying pathology: degenerative and functional. Degenerative MR is most often due to myxomatous degeneration and MV prolapse, and can result in a ruptured chordae and a flail leaflet segment. Pulmonary hypertension due to degenerative MR complicated by a flail leaflet is an independent predictor of freedom from death [all cause, HR 2.03 (1.30-3.18) P=0.002; and cardiovascular, HR 2.21 (1.30-3.76) P=0.003; and worsening heart failure, HR 1.70 (1.10-2.62) P=0.018] over a 4-year follow-up period.

Functional MR is due to dilation and/or dysfunction of the left ventricle, causing mitral annular dilation. A dilated mitral annulus causes papillary muscle displacement, poor leaflet mobility, tethered leaflets, resulting in poor leaflet coaptation and MR.
tension in the setting of functional MR increases mortality, even when controlling for the degree of LV dysfunction. Another percutaneous option is the MitraClip (Abbott Vascular, Santa Clara, CA), which is commercially available for degenerative (primary) 3 to 4+ MR in patients who are not candidates for surgery. The MitraClip is delivered anterograde across the MV via trans-septal approach to achieve an end-to-end repair of the MV leaflets. The pivotal trial leading to FDA approval of MitraClip was EVEREST II, which randomized patients 2:1 to MitraClip or MV surgery. Patients undergoing MitraClip had an improved safety profile, but less reduction in MR compared to surgery. Clinical outcomes were similar (LV size, NYHA functional class, quality of life measures) between the 2 groups. A large European registry of 628 patients demonstrated similar 1-year mortality rates with both functional and degenerative MR (15.3%), but an increased rate of heart failure admissions with functional MR (25.8% vs 12.0%, P[log-rank]=0.009). This study also showed a significant reduction in PASP from baseline to discharge and out to 1 year (functional MR: 44.2 mm Hg to 39.2 mm Hg and 40.5 mm Hg, respectively; and degenerative MR: 53.5 mm Hg to 43.4 mm Hg and 42.9 mm Hg, respectively). Matsumoto et al performed serial PASP measurements after MitraClip placement in 48 patients with PH (PASP >50 mm Hg) and 42 patients without PH. Patients with PH had a reduction at 30 days (63.5 ± 9.0 mm Hg to 50.0 ± 13.7 mm Hg), which was sustained at 1 year (50.8 ± 15.3 mm Hg). Preexisting PH was a predictor of 1-year mortality (HR 3.731, 95% CI 1.653 to 8.475, P=0.002). A large-scale randomized Phase 3 clinical trial for MitraClip is underway (COAPT, NCT01626079), which includes both functional and degenerative MR.

**Table 1. Mitral Regurgitation Based on Underlying Pathology.**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Degenerative</th>
<th>Functional</th>
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<tbody>
<tr>
<td>Mitral value prolapse</td>
<td>Dilation and/or dysfunction of the left ventricle, causing mitral annular dilation</td>
<td></td>
</tr>
<tr>
<td>Myxomatous degeneration</td>
<td>Repetured chordae</td>
<td>Papillary muscle displacement</td>
</tr>
<tr>
<td>Flail leaflet segment</td>
<td>Flail leaflet segment</td>
<td>Poor leaflet mobility</td>
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<tr>
<td>Tether leaflets</td>
<td>Poor leaflet coaptation and mitral regurgitation</td>
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**Pulmonary hypertension in this setting**

- In dependent predictor of death over 4 year follow-up period
- Increases mortality

Acute severe MR is rare, but most often occurs due to ruptured chordae with or without underlying endocarditis. Acute onset MR results in rapid increase in pulmonary venous pressure and pulmonary edema, often accompanied by systemic hypotension and tachycardia aimed at compensating for acute reduction in afterload.

Medical treatment for chronic degenerative MR is aimed at lowering LV afterload (angiotensin-converting enzyme inhibitor, ACE; or angiotensin receptor blockers, ARB), but has not been shown to reduce clinical event rates. On the other hand, there is a well-established survival benefit with guideline-directed therapy for chronic functional MR due to LV systolic dysfunction or ischemic cardiomyopathy. These medications include ACE/ARB, beta-blockers, and treatment for coronary artery disease when applicable. Cardiac resynchronization therapy with biventricular pacing should also be considered in patients with reduced ejection fraction, which has been shown to improve PAP in this subset of patients.

If symptoms persist (NYHA functional class II–IV) despite maximal medical therapy, surgical intervention is indicated for severe degenerative MR. In asymptomatic severe MR, surgery is indicated when the LV ejection fraction (LVEF) falls below normal (30% to 60%), LV dilatation develops, new onset atrial fibrillation appears, or upon development of PH (PASP >50 mm Hg at rest, or PASP >60 mm Hg with exercise). Surgery for chronic severe functional MR with an LVEF <30% should only be considered with refractory severe symptoms (NYHA functional class III–IV) despite optimal medical therapy. The role of MV surgery for functional MR is debated, as the underlying pathology is a poorly functioning dilated LV. In general, repair of the MV is preferred over replacement when valve anatomy is suitable, and should be performed in experienced centers.

Worsening LV function after MV surgery may be due to the increased LV afterload that develops after eliminating the MR, and may necessitate mechanical circulatory support (LVAD). Urgent surgical intervention is the only definitive treatment for acute severe MR, though afterload reduction with nitroprusside or intra-aortic balloon counterpulsation can help stabilize patients until surgery.

Several percutaneous options for MV repair have emerged in recent years. One type of device is implanted in the coronary sinus. The goal of this device is to reshape the contour of the MV annulus and improve leaflet coaptation in functional MR. Several of these devices have shown encouraging results in the proof of concept and feasibility stages, but have failed to translate into reproducible and durable clinical results. Coronary sinus implants have limited application for 3 primary reasons: 1) variability in the spatial relationship between the coronary sinus, fibrous trigones, and the mitral annulus; 2) ongoing mitral annular dilation will likely cause recurrent or worsening MR post procedure; and 3) the implant can cause coronary artery obstruction.

Aortic Stenosis

Etiologies of AS include calcification of a trileaflet or bicuspid aortic valve or rheumatic heart disease. The natural history of medically treated symptomatic AS is poor, with a 50% mortality rate over 2 years. Roughly two-thirds of patients with severe AS have concomitant PH. Similar to PH related to
MV disease, PH in AS increases mortality regardless of management strategy—medical, surgical, or percutaneous. The degree of PH appears to correlate with left atrial dysfunction and LV diastolic dysfunction. The benefit of vasodilators in asymptomatic very severe AS (AVA <0.7 cm², transaortic jet velocity of >5 m/sec, or transvalvular gradient of >60 mm Hg). Medical management until that point (or in patients deemed unfit for intervention) should focus on guideline-directed treatment of hypertension and hyperlipidemia. The most common method of assessing operative risk is the Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM), which does not incorporate PH. Alternatively, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) does consider PH in risk calculation. Of note, combined valve disease is not uncommon in this population (namely, concomitant MR). Surgery has long been the standard of care for those requiring aortic valve replacement (AVR), as valve repair for AS is feasible. Transcatheter aortic valve replacement (TAVR) has now emerged as a commercially available option worldwide for patients who are considered at prohibitive or high risk for surgical AVR. The 2 most widely used valves are the Edwards Sapien XT and S3 valves (balloon expandable) and the Medtronic CoreValve and Evolut R valves (self-expanding). There are ongoing trials that aim to expand the indications for TAVR to include those at moderate risk. Surgical AVR and TAVR have been identified as treatments for PH caused by LV outflow obstruction secondary to AS, both demonstrating a significant and durable reduction in PAP out to 1 year. The presence of new or worse PH post TAVR has been shown to increase mortality, a phenomenon that is most often related to perivalvular regurgitation. Our data have shown the importance of defining preprocedure PH in this population in order to tailor periprocedure medication and fluid management. Also, patients with a precapillary component can be expected to have less improvement in post-TAVR PH. 

### Aortic Regurgitation

Both aortic root and primary aortic valve abnormalities can result in aortic regurgitation (AR). Leaflet failure or perivalvular regurgitation of bioprosthetic aortic valves can result in AR as well. Chronic AR can be present for many years without symptoms or LV compromise, with the LV increasing total stroke volume to maintain normal CO. Eventually left atrial pressure increases, causing symptoms, and systolic dysfunction will develop, as compensatory LV hypertrophy is insufficient. As a result, pulmonary venous pressures will rise, causing PH (defined as PASP >60 mm Hg) in 24% of patients in a case series of 139 patients with severe chronic AR. While mild or moderate AR carries a good prognosis, severe AR will result in symptoms or LV dysfunction at a rate of 4.3% per year. Echocardiography remains the central tool for evaluation, which, in addition to PAP estimation, provides quantitative assessment such as regurgitation volume, regurgitant fraction, and effective regurgitant orifice area. When echocardiography is suboptimal, magnetic resonance imaging (MRI) can be considered.

Vasodilators (nifedipine, ACE) are the primary medical intervention for patients with AR and diastolic hypertension, while beta blockade should be avoided. The benefit of vasodilators in asymptomatic patients with severe AR is not clear. Central to the management of AR is root or valve intervention prior to development of irreversible LV dysfunction. Aortic valve replacement in chronic AR has been shown to effectively reduce PVR (4.7 ± 3.5 to 1.5 ± 0.8 Wood units) and normalize PASP in a series of 139 patients from Naidoo et al. While chronic AR can be monitored until symptoms or LV dysfunction develop, acute severe AR requires emergent surgical intervention.

### CONCLUSION

With an aging population, VHD and WHO 2 PH are increasingly prevalent and warrant an experienced team in addressing the specifics of intervention. This patient population carries a higher procedural risk, but intervention is the only chance for improvement. Our data show the feasibility and importance of approaching this cohort with a multidisciplinary team pre- and postintervention. One should identify those patients that need targeted pulmonary vasodilators, either due to existence of precapillary PH from systemic scleroderma or lung disease, or due to the more severe CPpPH. Postprocedural management of PH must be guided by defining components of prior interventions.

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