The Right Ventricle: A Not-So-Innocent Bystander in Pulmonary Hypertension Due to Left Heart Disease

Brian A. Houston, MD
Division of Cardiology
Department of Medicine
The Johns Hopkins School of Medicine
Baltimore, MD

Steven Hsu, MD
Division of Cardiology
Department of Medicine
The Johns Hopkins School of Medicine
Baltimore, MD

Emmanouil Tampakakis, MD
Division of Cardiology
Department of Medicine
The Johns Hopkins School of Medicine
Baltimore, MD

Ryan J. Tedford, MD
Division of Cardiology
Department of Medicine
The Johns Hopkins School of Medicine
Baltimore, MD

The most common disease associated with high pulmonary vascular pressures and right ventricular (RV) afterload is left heart disease (LHD). In this review, we will discuss the role right heart disease (RHD) plays in LHD progression, prognosis, and treatment. We will first discuss the current definitions employed in RHD and its epidemiology in various left heart diseases. We will next explore the pathophysiology of RV dysfunction in LHD, including a discussion of the effects and components of RV afterload and RV/left ventricular contractile interactions. Finally, we will describe the recently observed clinical implications of RV dysfunction in LHD and pertinent therapeutic considerations.

"After all, there are no innocent bystanders . . . what are they doing there in the first place?"
—William S. Burroughs, "Exterminator!"

Contemporary cardiologists have loudly decried the disregard with which the right ventricle (RV) was historically held. In the early 17th century, Sir William Harvey proclaimed, "the right ventricle may be said to be made for the sake of transmitting blood through the lungs, not for nourishing them."[1] However, between then and the late 20th century, the RV was largely ignored. Indeed, the most striking scientific findings concerning the RV were by investigators who sclerosed the RV in dogs[2] and completely bypassed the RV in humans[3] only to find that circulation continued relatively unimpeded. Thus, the RV was relegated to the status of an innocent bystander in cardiac disease. We now know, of course, that cardiologists of the early 20th century would have been well-served to ask just what the RV was "doing there in the first place." As cardiac surgery became more prevalent, surgeons began anecdotally noting the importance of right-sided function in predicting patient outcomes during and after surgery. In the 1980s, investigators realized that while a damaged or bypassed RV can support circulation in the face of low afterload, RV function plays an increasingly crucial role in the presence of any disease state associated with elevated afterload.[4] It became clear that with any elevation in afterload, the RV becomes a not-so-innocent bystander.

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Correspondence: Ryan.Tedford@jhmi.edu
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DEFINITIONS

The International Right Heart Foundation Working Group recently proposed a comprehensive definition of right heart failure as: "a clinical syndrome due to an alteration of structure and/or function of the right heart circu-

latory system that leads to suboptimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures—at rest or with exercise."[5] Although the RV is a key component of the right heart system (and our focus), it is important to remember that unfavorable alterations of any component of the circulation from the systemic veins up to the pulmonary capillaries can result in right heart failure symptoms.

Similar to the left ventricle (LV), the 3 determinants of RV function are preload, contractility, and afterload. Defining afterload is particularly important as the presence of elevated RV afterload in left heart disease (LHD) identifies an "RV at risk." For this reason, much attention has been placed on defining pulmonary hypertension (PH) in the context of LHD. Currently, PH is defined by a resting mean pulmonary artery pressure (mPAP) that is greater than or equal to 25 mm Hg.[4] Mean PAP is a function of the product of cardiac output (CO) and pulmonary vascular resistance (PVR) as well as the downstream left heart pressure (pulmonary artery wedge pressure [PAWP]/left atrial pressure [LAP] or left ventricular end-diastolic pressure [LVEDP]):

$$mPAP = PVR \times CO + PAWP$$

Thus, one can see that mPAP may be elevated due to increase in resistance, an increase in flow (CO), or a downstream increase in left heart filling pressure. In cases of LHD, the latter variable predominates, though we will discuss later how it can also contribute to acute and chronic alterations in PVR and capacitance.

The relative contributions of these various components to an elevated mPAP in a given patient carries prognostic and diagnostic information, so considerable attention has been paid to the nomenclature employed to categorize differing hemodynamic profiles. Recently, the Fifth World Symposium on Pulmonary Hypertension proposed the following: 1) isolated postcapillary PH (IpcPH)—previously termed "passive" PH; and 2) combined postcapillary and precapillary PH (CpcPH)—previously called "reactive," "out-of-proportion," or "mixed PH."[6] IpcPH and CpcPH are differentiated hemodynamically by parameters that suggest a component of pulmonary vascular disease (ie, a precapillary component). Commonly used parameters to differentiate between IpcPH and CpcPH include the transpulmonary gradient (TPG), which is the mPAP minus PAWP, PVR (TPG divided by CO), and the diastolic pulmonary gradient (DPG) [diastolic pulmonary artery pressure (dPAP) minus PAWP] (Table 1). Although initially proposed as the sole discriminator of CpcPH and IpcPH, more recent studies have suggested the DPG may not carry the prognostic significance originally thought,[7-11] casting doubt on its inclusion in diagnostic definitions.

Table 1.

	Hemodynamic profiles	
	IpcPH	CpcPH
PAWP	>15 mm Hg	>15 mm Hg
DPG	<7 mm Hg	≥7 mm Hg
TPG	≤12 mm Hg	>12 mm Hg
PVR	<3 mm Hg	≥3 mm Hg

EPIDEMIOLOGY

Before delving into the details of right heart disease (RHD) pathophysiology, it is important to identify the extent to which LHD patients are affected by RHD. However, quantification of the prevalence of elevated pulmonary pressure (PH) in LHD carries important caveats. First, most large studies have employed echocardiography in estimating systolic pulmonary artery pressure (sPAP) even though mPAP is the true hemodynamic determinant of the presence of PH. While mPAP can be derived from sPAP with a relative degree of reliability,[12,13] echocardiographic measurement of sPAP remains an inexact technique[14,15] and requires an adequate tricuspid regurgitation jet. While more precise, retrospective studies employing hemodynamic data are susceptible to referral bias and inadequate fluid optimization status and could overestimate the prevalence of PH in LHD.

Even accounting for these limitations, it is clear that PH in LHD is a prevalent condition. In patients with heart failure with reduced ejection fraction (HFrEF), studies indicate that 26% to 86% of patients have PH.[16-19] The prevalence of CpcPH in HFrEF patients ranges from 25% to 47%: a recent evaluation of a large ambulatory HFrEF population found 40% with CpcPH.[19] In patients with heart failure with preserved ejection fraction (HFpEF), the prevalence of PH has ranged from 36% to 83%.[20-22] Data are more limited on the prevalence of CpcPH in HFpEF. Using a precapillary component definition of PVR >2.5 Wood units or TPG>12 mm Hg, Thenappan found a prevalence of 68% among those patients in their PH registry who had undergone right heart catheterization.[23] Given the heterogeneity of HFpEF, vast differences in population demographics present in various publications may also affect the reported prevalence of PH.[12,24,25] Finally, PH is prevalent in patients with left-sided valvular disease, including mitral stenosis (up to 73%),[26,27] mitral regurgitation (23%–44%),[28,29] and aortic stenosis (29%–47%).[30-32]

PATHOPHYSIOLOGY OF RHD IN LHD

Mechanisms of PH in LHD (Increasing RV Afterload)

In LHD, the inciting abnormality leading to PH is an elevation in LAP, whether due to HFrEF, HFpEF, or valvular disease. This leads to a passive proportional increase in dPAP (and thus mPAP), which results in PH even in the absence of alterations in the pulmonary vasculature.[33] However, the pathophysiology is often more complex than simple passive elevation in pressure. Even in the absence of structural pulmonary vascular changes, passive elevations in pulmonary vascular pressure may contribute to a perceived precapillary component to PH. Unlike in the systemic circulation, compliance (or the blood storage capacity of the vessels) in the pulmonary vasculature is more evenly distributed across the pulmonary bed, and the peripheral or distal vessels are responsible for most of the pulmonary vascular compliance.[34,35]

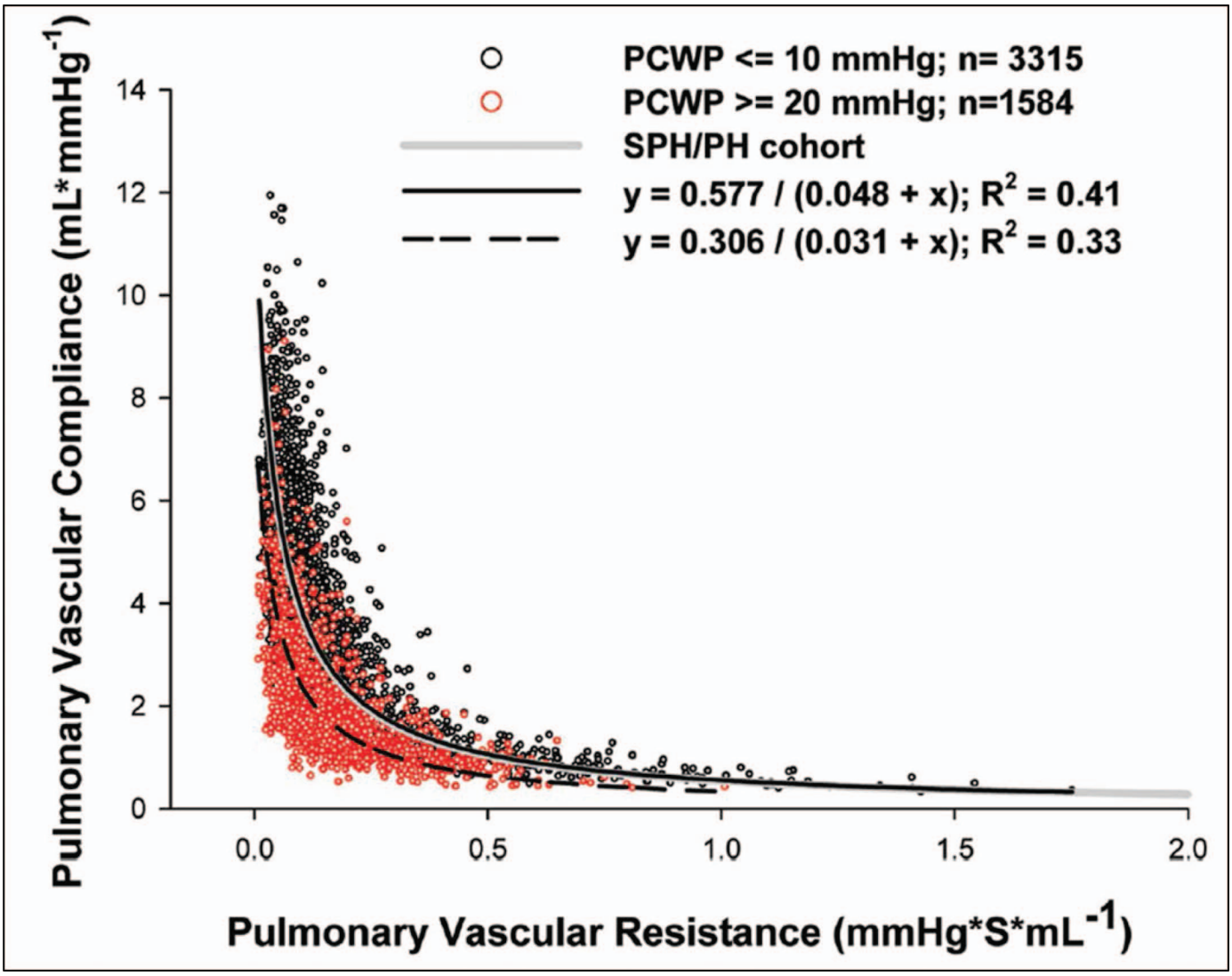

Figure 1: Plot of pulmonary vascular resistance vs pulmonary vascular compliance, showing an inverse hyperbolic relationship between the 2 determinants of afterload. The relationship in those normal left heart filling pressures (black dots and solid black line) is identical to a cohort of patients with known or suspected pulmonary arterial hypertension (grey line). With elevations in left heart filling pressures (those with pulmonary artery wedge pressure >20; red dots), the curve shifts downward indicating lower pulmonary vascular compliance at a given resistance, and increases in RV pulsatile load. Used with permission from Tedford et al. *Circulation*. 2012;125(2):289-297.

Thus, the principal determinant of pulmonary vascular compliance is usually PVR, with compliance declining in a predictable hyperbolic fashion as PVR rises.[36-38] Elevations in left-sided pressure significantly alter this paradigmatic relationship (Figure 1). As passive pressure increases, compliance declines at a given PVR, leading to enhanced pulmonary wave reflections. These reflective waves return during ventricular systole to further increase sPAP. Because dPAP is unaffected by wave reflections, the TPG and PVR increase.[39,40]

With further elevation in pulmonary pressures, alterations in pulmonary vasoreactivity and structural damage ensue. Smooth muscle vascular relaxation is impaired, likely arising from endothelial dysfunction due to alterations in the nitric oxide,[41] endothelin,[42-44] and renin-angiotensin-aldosterone signaling pathways.[45] Further, elevated pulmonary vascular pressure results in damage to the pulmonary capillaries. While plexiform lesions (the pathologic correlates of World Health Organization [WHO] Group 1 PH) are notably absent,[46,47] with sustained injury, deposition of type IV collagen increases, and alterations occur in endothelial cell plasma membranes, cytoskeletal components, calcium handling, and expression of various growth factors.[48-52] This contributes to physical alveolar-capillary remodeling and impairments in alveolar gas exchange.[53] Further, chronic pressure elevations are associated with increased muscularization of the pulmonary arterioles and medial hypertrophy and neointima formation in the pulmonary arteries and veins.[46,47] All of these changes result in elevations in PVR and a pathologic transition from IpcPH to CpcPH. While improvement in PVR has been described after procedures reducing left-sided pressures (eg, mitral valve surgery, left ventricular assist device), many patients have persistent elevations in PVR, which supports the persistence of these pathologic changes to the PVR.[54-57] The degree, timing, and prediction of the regression of these

pathologic changes remains poorly understood.

Response of the RV to Elevated Afterload

RV afterload is defined by ventricular wall stress occurring throughout ejection. LaPlace's law defines wall stress (σ) mathematically as a proportionality between ventricular pressure during ejection (P_{EJ}) multiplied by the ventricular radius of curvature (r_{EJ}) divided by the wall thickness (h).[58]

$$\sigma \propto \frac{P_{EJ} \cdot r_{EJ}}{h}$$

When considering wall stress, 2 important differences between the LV and RV must be considered. First, the RV is a thin-walled structure, so "h" in LaPlace's equation is a small number even during systole. Second, while the radius of curvature (r_{EJ}) declines throughout systole in the LV, mitigating to some extent the increase in pressure, the r_{EJ} declines less (or may actually increase) in the RV during systole.[59] Therefore, RV wall stress is highly dependent on and can be estimated by the pressure (P_{EJ}). By integrating the RV systolic pressure over the time between pulmonary valve opening and closing (ejection), one can accurately calculate P_{EJ}. Finally, by dividing the end-systolic pressure (ESP) by the stroke volume (SV), one can calculate a validated "lumped" parameter of afterload known as the effective arterial elastance (Ea). In normal subjects, the RV pressure-volume loop is triangular as pressure decays throughout ejection into a compliant vascular circuit. This makes determination of end-systolic pressure on routinely employed invasive (right heart catheterization) or noninvasive (echocardiography) assessment difficult. However, in diseases leading to elevated pulmonary pressures (eg, LHD), the reduction in compliance leads to an increase in pulsatile loading (due to augmented early return of arterial wave reflections) and a rise in pressure throughout ejection.[39,60] Thus, ESP may be closely approximated by peak sPAP (a value easily measured on right heart catheterization), and Ea calculated by sPAP divided by SV (Figure 2).

The RV LaPlace relationship described above would predict that RV function would be sensitive to acute increases in pulmonary pressures. Indeed, in a dog model, Abel et al found that an acute increase in mPAP of a mere 10–15 mm Hg resulted in a 30% reduction in right ventricular SV, while a 40 mm Hg increase in mean system arterial pressure only resulted in a 10% reduction in left ventricular SV.[61] This was paralleled in findings by Ghio et al where RV ejection fraction (RVEF) was inversely proportional to mPAP in 377 chronic heart failure patients.[62]

RV Contractile Adaptation and LV/RV Contractile Interactions

While the RV is quite sensitive to acute changes in pulmonary pressures, changes may occur over time to improve contractility, matching increases in afterload. While the beat-to-beat adaptation of ventricular contractile function based on preload (heterometric adaptation, described by Starling's law) is well-appreciated, the RV may also experience augmentation of contractile function with increased afterload conditions (eg, elevated Ea) over time, termed homeometric adaptation and described by Anrep's law of the heart.[63] In a normal RV, elevations in afterload are matched by homeometric elevations in contractile function and perhaps even adaptive hypertrophy, and the RV and its afterload remain well "coupled." However, many diseases that affect the left heart respect no septal boundary and may lead to intrinsic RV contractile dysfunction as well. Furthermore, contraction against a chronically elevated afterload leads to adverse RV remodeling (maladaptive hypertrophy, dilation, and ultimately contractile failure). In these cases, RV contractile function cannot augment to match an elevated afterload (it is "uncoupled" from its afterload),[60] and either stroke volume must decline or preload must increase to take advantage of heterometric adaptation to maintain CO.

Finally, it must be understood that the left and right ventricles do not exist in isolation, and are instead highly interdependent. In an elegant set of experiments in the early 1990s involving electrically isolated canine ventricles, Damiano et al demonstrated that approximately 30% to 50% of RV contractile energy is generated by LV contraction.[4] More recently, experiments have suggested that septal function is essential for RV longitudinal contraction, which contributes up to 80% of RV systolic function.[64] Therefore, one can appreciate that even in the absence of any intrinsic RV disease, compromise of the LV and/or the interventricular septum (as commonly occurs in LHD) will result in a reduction in the contractile function of the RV.

CLINICAL AND THERAPEUTIC IMPLICATIONS OF RHD IN VARIOUS LHD STATES

Heart Failure

In a study of 463 patients with HFrEF undergoing hemodynamic catheterization, Miller et al found that the presence of any PH was correlated with an elevated risk of death (adjusted HR 2.24, $P<0.001$).[65] Furthermore, patients with a PVR ≥3 Woods units (termed "mixed PH" in this study) had a significantly elevated risk of death compared with those patients with a PVR <3 ("passive PH"), thus establishing the prognostic import of RV afterload in LHD, and specifically the poor prognosis portended by HF patients with PH and significant precapillary component. Several studies had previously established that HFrEF patients with reduced RV function (defined primarily by echocardiographically derived parameters) carried a worse prognosis. In 2001, Ghio and colleagues studied the additive prognostic value of combining measures of RV afterload (mPAP) and RV systolic function (thermodilution-derived RVEF) in 377 patients with heart failure undergoing hemodynamic catheterization. In this study, patients with elevated mPAP and preserved RVEF comprised a small portion of the population, but had a similar prognosis to patients with a normal mPAP. Patients with an elevated mPAP and reduced RVEF were over 7 times more likely to die or undergo urgent transplantation when compared with patients with normal RVEF and

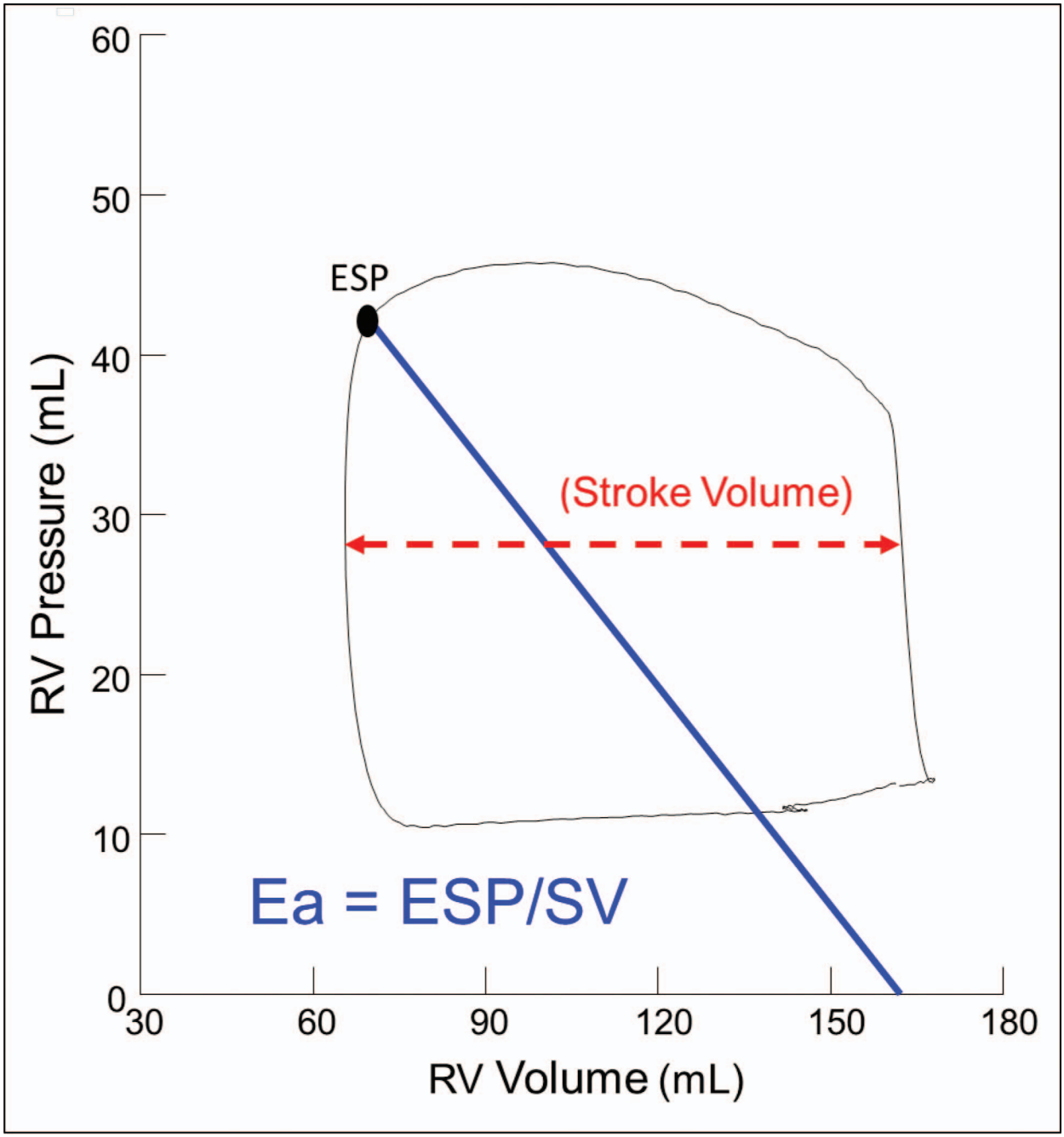

Figure 2: Right Ventricular Pressure Volume (PV) Loop from a patient with mild pulmonary hypertension due to heart failure with preserved ejection fraction. The width of the PV loop is the stroke volume (SV; red-dotted line). Due to the shape of the PV loop with pulmonary hypertension, end-systolic pressure (ESP) is closely approximated by peak pulmonary artery systolic pressure. Effective arterial elastance (blue line), a "lumped" parameter of afterload, can then be estimated as systolic pulmonary artery pressure divided by SV.

normal mPAP.[62] This finding highlights that neither RV function nor pulmonary pressures should be considered in isolation; it is the inability of the RV to remain coupled to its afterload that likely drives disease progression.

For patients with HFpEF, elevated pulmonary pressures carry a worse prognosis as well. In a heart failure cohort with both HFpEF and HFrEF patients, Bursi found increasing tertiles of echocardiographically derived sPAP to be associated with worse survival, independent of LV ejection fraction (LVEF).[66] In 2014, Melenovsky and colleagues identified RV dysfunction as the strongest predictor of death in an HFpEF population.[67] Later the same year, Mohammed and colleagues demonstrated that the addition of RV dysfunction (defined by semiquantitative echocardiographic assessment) to elevated afterload carries an increased risk of mortality and hospitalization, similar to HFrEF.[68]

When considering therapy of RHD in the setting of heart failure, one must remember the contribution of elevated left atrial pressure to RV afterload. As PAWP rises, not only does dPAP passively increase, but pulsatile RV load also increases, leading to out-of-proportion elevations in sPAP, TPG, and PVR as described above. Dupont and colleagues

found that pulmonary artery compliance (estimated as SV/pulmonary pulse pressure) was a better predictor of both RV dysfunction as well as transplant-free survival than PVR.[69] The authors suggested that compliance (like Ea) lumps both resistive (PVR) and pulsatile components into a single measure of RV load. Compliance was also recently shown to predict survival in those heart failure patients with normal PVR.[40] These studies may suggest that measures of total RV afterload, rather than specifically the precapillary component, are the best hemodynamic predictors of survival in heart failure, and further support the notion that RV function and load influence outcome in left heart failure. Therefore, the importance of adequately treating elevated left heart filling pressures to improve RV afterload and contractile efficiency cannot be overstated. Similarly, therapeutic decisions dependent on measures of RV afterload (eg, heart transplantation for patients with elevated PVR) should only be based on hemodynamics obtained when the left heart filling pressures are optimally treated. To assess and treat RHD in left heart failure, one must first maximally treat the failing left heart.

For patients with continued elevations in RV afterload despite optimization of left heart filling pressures, evidence-based therapeutic options are limited. Given the afterload sensitivity of the RV and the poor prognosis portended by elevated PVR in heart failure, it seems logical that a pharmacologic reduction in the precapillary component of RV afterload would benefit patients with heart failure. Phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil inhibit degradation of cyclic guanosine monophosphate, enhancing signaling through the nitric oxide pathway, and seem tailor-made for therapy of heart failure complicated by RHD. Indeed, early studies showed great promise for sildenafil in both HFrEF and heart failure.[70-74] However, the RELAX study, a multicenter, double-blind, placebo-controlled, parallel-group, randomized clinical trial of 216 stable outpatients with HFpEF, found that sildenafil did not improve exercise capacity or clinical status compared with placebo.[75] In a substudy of RELAX, Borlaug and colleagues shed light on a potential mechanism of this finding by demonstrating that while sildenafil improved endothelial function and reduced systemic load, it was associated with a reduction in LV contractility and ultimately had no effect on pulmonary artery systolic pressure in these patients.[76]

Other PH-specific pharmacologic agents studied in LHD have met with even more disappointing results. The FIRST study, a multicenter, international, randomized study in 471 HFrEF patients, demonstrated that epoprostenol failed to improve exercise capacity or quality of life and was terminated early due to a strong trend toward decreased survival.[77] Echoing the PDE-5 experience, endothelin-1 antagonists such as bosentan showed early promise in animal and small hemodynamic studies of patients with PH-LHD.[78,79] However, in the large-scale REACH clinical trial, bosentan therapy failed to improve outcomes and was instead associated with a higher early risk of heart failure events.[80] Importantly, no multicenter randomized study has exclusively enrolled heart failure patients with a significant precapillary component, and it remains unknown if PH-specific therapy could benefit this population.

Recently, Borlaug and colleagues demonstrated the administration of dobutamine (a β-1 agonist) to HFpEF patients resulted in improvements in RVEF. Surprisingly, however, they were able to demonstrate that this improvement was solely due to reduction in RV afterload unrelated to reduction in left heart pressures, suggesting that these HFpEF patients had an underlying reversible pulmonary vasoconstriction that is responsive to β-adrenergic therapy.[81] This suggests a potentially novel direction for pharmacologic therapy for RHD in HFpEF patients, though prior experience with β-adrenergic stimulatory therapy in heart failure advises caution.[82]

Left-sided Valvular Disease

Mitral stenosis represents the paradigmatic left-sided valvular disease associated with the development of PH. Fortunately, correction of the underlying valvular disease usually results in resolution of PH, though improvement may take up to a year to be evident.[83,84] Young patients with a shorter duration of disease tend to demonstrate more marked improvement, perhaps due to the absence of truly irreversible pulmonary vascular changes. Preoperative severity of PH does not affect outcomes in patients undergoing balloon mitral valvuloplasty, and even patients with very high pulmonary pressures (mPAP >50 mm Hg) may undergo mitral valve replacement surgery with resultant postoperative improvements in pulmonary vascular hemodynamics.[85] Aortic stenosis is also associated with the development of PH, and correction of the underlying valvular disorder is similarly associated with an improvement in pulmonary hemodynamics. Even in patients with severe PH (sPAP >60 mm Hg), recent studies show benefit for aortic valve replacement.[86]

LV Assist Device Therapy

With the growing heart failure population and continued scarcity of suitable transplant organs, left ventricular assist device (LVAD) therapy is becoming increasingly common as both a bridge to transplant and long-term treatment option for end-stage heart failure. While LVAD therapy reduces RV afterload by lowering the left heart filling pressures, up to 40% of patients experience clinical right heart failure after LVAD implantation,[87] and right heart failure is associated with increased mortality post-LVAD.[88] The explanations for the observed RV failure are myriad and include damage to the RV and septum during surgery, disadvantageous changes in ventricular interdependence mitigated by reduced LV contractility, changes in septal architecture, and alterations in RV shape all in the setting of a suddenly elevated CO.[89-92] Therefore, in patients being considered for LVAD implantation, careful preoperative consideration of RV function is crucial to avoid potentially catastrophic post-LVAD RV failure.

In surgeries involving cardiopulmonary bypass and pericardiotomy (such as traditional LVAD implantation), Raina demonstrated that the RV alters its con-

tractile pattern from longitudinal to transverse, though overall RV function remained normal in the face of normal afterload.[93] It has been postulated that the transverse RV contractile pattern is more sensitive to alterations in afterload, and indeed a retrospective hemodynamic analysis from our group showed that the RV has an increased sensitivity to afterload in LVAD patients.[94] Furthermore, it appears that while RV function worsens immediately after LVAD implantation, it improves over the ensuing 12 to 36 months in a manner almost wholly dependent on a concomitant improvement in RV afterload. Thus, in the patient struggling with post-LVAD RV failure, aggressive afterload reduction and "tincture of time" may lead to improvements in RV function.

CONCLUSION

Right heart disease is common in left heart disease and carries important prognostic implications. When assessing patients with RHD in the context of LHD, one must consider the contributions of both postcapillary and precapillary components of RV afterload, remembering that postcapillary components (elevated PAWP)—in addition to passive elevations in pressure—can cause augmented pulsatile loading of the RV out of proportion to the PVR. Therapy of RHD in LHD should focus first on maximally treating the respective left heart condition and then considering therapeutic options to reduce RV afterload or potentially augment contractility. In every variety of LHD, one must remember that the RV is not an innocent bystander, but is an active player in the game.

References

1. Harvey W. Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus. 1628.
2. Starr I, Jeffers WA, Meade RH. The absence of conspicuous increments of venous pressure after severe damage to the right ventricle of the dog, with discussion of the relation between clinical congestive failure and heart disease. *Am Heart J*. 1943;26(3):291.
3. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26(3):240-248.
4. Damiano RJ Jr, La Follette P Jr, Cox JL, Lowe JE, Santamore WP. Significant left ventricular contribution to right ventricular systolic function. *Am J Physiol*. 1991;261(5 Pt 2):H1514-H1524.
5. Mehra MR, Park MH, Landzberg MJ, Lala A, Waxman AB. Right heart failure: toward a common language. *Pulm Circ*. 2013;3(4):963-967.
6. Vachiéry J, Adir Y, Barberà JA, et al. Pulmonary hypertension due to left heart diseases. *J Am Coll Cardiol*. 2013;62(25 Suppl):D100-D108.
7. Tampakakis E, Leary PJ, Selby VN, et al. The diastolic pulmonary gradient does not predict survival in patients with pulmonary hypertension due to left heart disease. *JACC Heart Fail*. 2015;3(1):9-16.
8. Tedford RJ, Beaty CA, Mathai SC, et al. Prognostic value of the pre-transplant diastolic pulmonary artery pressure-to-pulmonary capillary wedge pressure gradient in cardiac transplant recipients with pulmonary hypertension. *J Heart Lung Transplant*. 2014;33(3):289-297.
9. Al-Naamani N, Prestion IR, Paulus JK, Hill NS, Roberts KE. Pulmonary Arterial Capacitance Is an Important Predictor of Mortality in Heart Failure With a Preserved Ejection Fraction. *JACC Heart Fail*. 2015;3(6):467-474.
10. Selby VN, Vachiery J, Fang JC, et al. The Diastolic Pulmonary Gradient as a Predictor of Adverse Outcomes in Patients With Acute Decompensated Heart Failure. *J Heart Lung Transplant*. 2014;33(4 Suppl):S40.
11. Tampakakis E, Tedford RJ. Reply: characterization of pulmonary hypertension in heart failure using the diastolic pressure gradient: the conundrum of high and low diastolic pulmonary gradient. *JACC Heart Fail*. 2015;3(5):426-427.
12. Chemla D, Castelain V, Provencher S, Humbert M, Simonneau G, Hervé P. Evaluation of various empirical formulas for estimating mean pulmonary artery pressure by using systolic pulmonary artery pressure in adults. *Chest*. 2009;135(3):760-768.
13. Kind T, Faes TJ, Vonk-Noordegraaf A, Westerhof N. Proportional relations between systolic, diastolic and mean pulmonary artery pressure are explained by vascular properties. *Cardiovasc Eng Technol*. 2011;2(1):15-23.
14. Arcasoy SM, Christie JD, Ferrari VA, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med*. 2003;167(5):735-740.
15. Fisher MR, Forfia PR, Chamera E, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179(7):615-621.
16. Cappola TP, Felker GM, Kao WH, Hare JM, Baughman KL, Kasper EK. Pulmonary hypertension and risk of death in cardiomyopathy: patients with myocarditis are at higher risk. *Circulation*. 2002;105(14):1663-1668.
17. Khush KK, Tasissa G, Butler J, McGlothlin D, De Marco T; ESCAPE Investigators. Effect of pulmonary hypertension on clinical outcomes in advanced heart failure: analysis of the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) database. *Am Heart J*. 2009;157(6):1026-1034.
18. Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure. *Circ Heart Fail*. 2011;4(5):644-650.
19. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail*. 2013;1(4):290-299.
20. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol*. 2009;53(13):1119-1126.
21. Guazzi M, Borlaug BA. Pulmonary hypertension due to left heart disease. *Circulation*. 2012;126(8):975-990.
22. Burke MA, Katz DH, Beussink L, et al. Prognostic importance of pathophysiologic markers in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2013;7(2):288-299.
23. Thenappan T, Shah SJ, Gomberg-Maitland M, et al. Clinical characteristics of pulmonary hypertension in patients with heart failure and preserved ejection fraction. *Circ Heart Fail*. 2011;4(3):257-265.
24. Shah SJ. Matchmaking for the optimization of clinical trials of heart failure with preserved ejection fraction: no laughing matter. *J Am Coll Cardiol*. 2013;62(15):1339-1342.
25. Klapholz M, Maurer M, Lowe AM, et al; New York Heart Failure Consortium. Hospitalization for heart failure in the presence of a normal left ventricular ejection fraction: results of the New York Heart Failure Registry. *J Am Coll Cardiol*. 2004;43(8):1432-1438.
26. American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114(5):e84-e231.
27. Hart SA, Krasuski RA, Wang A, Kisslo K, Harrison JK, Bashore TM. Pulmonary hypertension and elevated transpulmonary gradient in patients with mitral stenosis. *J Heart Valve Dis*. 2010;19(6):708-715.
28. Saraiva RM, Yamano T, Matsumura Y, et al. Left atrial function assessed by real-time 3-dimensional echocardiography is related to right ventricular systolic pressure in chronic mitral regurgitation. *Am Heart J*. 2009;158(2):309-316.
29. Barbieri A, Bursi F, Grigioni F, et al; Mitral Regurgitation International DAtabase (MIDA) Investigators. Prognostic and therapeutic implications of pulmonary hypertension complicating

degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. *Eur Heart J*. 2011;32(6):751-759.
30. Silver K, Aurigemma G, Krendel S, Barry N, Ockene I, Alpert J. Pulmonary artery hypertension in severe aortic stenosis: incidence and mechanism. *Am Heart J*. 1993;125(1):146-150.
31. Melby SJ, Moon MR, Lindman BR, Bailey MS, Hill LL, Damiano RJ Jr. Impact of pulmonary hypertension on outcomes after aortic valve replacement for aortic valve stenosis. *J Thorac Cardiovasc Surg*. 2011;141(6):1424-1430.
32. Johnson LW, Hapanowicz MB, Buonanno C, Bowser MA, Marvasti MA, Parker FB Jr. Pulmonary hypertension in isolated aortic stenosis. Hemodynamic correlations and follow-up. *J Thorac Cardiovasc Surg*. 1988;95(4):603-607.
33. Harvey RM, Enson Y, Ferrer MI. A reconsideration of the origins of pulmonary hypertension. *Chest*. 1971;59(1):82-94.
34. Sipkema P, Latham RD, Westerhof N, Rubal BJ, Slife DM. Isolated aorta setup for hemodynamic studies. *Ann Biomed Eng*. 1990; 18(5):491-503.
35. Saouti N, Westerhof N, Helderman F, et al. RC time constant of single lung equals that of both lungs together: a study in chronic thromboembolic pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2009;297(6):H2154-H2160.
36. Lankhaar JW, Westerhof N, Faes TJ, et al. Quantification of right ventricular afterload in patients with and without pulmonary hypertension. *Am J Physiol Heart Circ Physiol*. 2006;291(4): H1731-H1737.
37. Lankhaar JW, Westerhof N, Faes TJ, et al. Pulmonary vascular resistance and compliance stay inversely related during treatment of pulmonary hypertension. *Eur Heart J*. 2008;29(13):1688-1695.
38. Bonderman D, Martischnig AM, Vonbank K, et al. Right ventricular load at exercise is a cause of persistent exercise limitation in patients with normal resting pulmonary vascular resistance after pulmonary endarterectomy. *Chest*. 2011;139(1):122-127.
39. Tedford RJ, Hassoun PM, Mathai SC, et al. Pulmonary capillary wedge pressure augments right ventricular pulsatile loading. *Circulation*. 2012; 125(2):289-297.
40. Pellegrini P, Rossi A, Pasotti M, et al. Prognostic relevance of pulmonary arterial compliance in patients with chronic heart failure. *Chest*. 2014; 145(5):1064-1070.
41. Cooper CJ, Jevnikar FW, Walsh T, Dickinson J, Mouhaffel A, Selwyn AP. The influence of basal nitric oxide activity on pulmonary vascular resistance in patients with congestive heart failure. *Am J Cardiol*. 1998;82(5):609-614.
42. Cody RJ, Haas GJ, Binkley PF, Capers Q, Kelley R. Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. *Circulation*. 1992; 85(2):504-509.
43. Tsutamoto T, Wada A, Maeda Y, Adachi T, Kinoshita M. Relation between endothelin-1 spillover in the lungs and pulmonary vascular resistance in patients with chronic heart failure. *J Am Coll Cardiol*. 1994;23(6):1427-1433.
44. Giaid A, Yanagisawa M, Langleben D, et al. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med*. 1993; 328(24):1732-1739.
45. Cargill RI, Lipworth BJ. Lisinopril attenuates acute hypoxic pulmonary vasoconstriction in humans. *Chest*. 1996;109(2):424-429.
46. Delgado JF, Conde E, Sánchez V, et al. Pulmonary vascular remodeling in pulmonary hypertension due to chronic heart failure. *Eur J Heart Fail*. 2005;7(6):1011-1016.
47. Rich S, Rabinovitch M. Diagnosis and treatment of secondary (non-category 1) pulmonary hypertension. *Circulation*. 2008;118(21):2190-2199.
48. Townsley MI, Fu Z, Mathieu-Costello O, West JB. Pulmonary microvascular permeability. Responses to high vascular pressure after induction of pacing-induced heart failure in dogs. *Circ Res*. 1995;77(2):317-325.
49. Lee YS. Electron microscopic studies on the alveolar-capillary barrier in the patients of chronic pulmonary edema. *Jpn Circ J*. 1979;43(10):945-954.
50. Negrini D, Passi A, de Luca G, Miserocchi G. Pulmonary interstitial pressure and proteoglycans during development of pulmonary edema. *Am J Physiol*. 1996;270(6 Pt 2):H2000–H2007.
51. Palestini P, Calvi C, Conforti E, Botto L, Fenoglio C, Miserocchi G. Composition, biophysical properties, and morphometry of plasma membranes in pulmonary interstitial edema. *Am J Physiol Lung Cell Mol Physiol*. 2002;282(6):L1382-L1390.
52. Kerem A, Yin J, Kaestle SM, et al. Lung endothelial dysfunction in congestive heart failure: role of impaired Ca2+ signaling and cytoskeletal reorganization. *Circ Res*. 2010;106(6):1103-1116.
53. Guazzi M. Alveolar gas diffusion abnormalities in heart failure. *J Card Fail*. 2008;14(8): 695-702.
54. Cámara ML, Aris A, Padró JM, Caralps JM. Long-term results of mitral valve surgery in patients with severe pulmonary hypertension. *Ann Thorac Surg*. 1988;45(2):133-136.
55. Klotz S, Wenzelburger F, Stypmann J, et al. Reversible pulmonary hypertension in heart transplant candidates: to transplant or not to transplant. *Ann Thorac Surg*. 2006;82(5):1770-1773.
56. Morgan JA, Paone G, Nemeh HW, et al. Impact of continuous-flow left ventricular assist device support on right ventricular function. *J Heart Lung Transplant*. 2013;32(4):398-403.
57. Mikus E, Stepanenko A, Krabatsch T, et al. Reversibility of fixed pulmonary hypertension in left ventricular assist device support recipients. *Eur J Cardiothorac Surg*. 2011;40(4):971-977.
58. Stillwell GK. The Law of Laplace. Some clinical applications. *Mayo Clin Proc*. 1973;48(12): 863-869.
59. Greyson CR. The right ventricle and pulmonary circulation: basic concepts. *Rev Esp Cardiol*. 2010;63(1):81-95.
60. Tedford RJ, Mudd JO, Girgis RE, et al. Right ventricular dysfunction in systemic sclerosis-associated pulmonary arterial hypertension. *Circ Heart Fail*. 2013;6(5):953-963.
61. Abel FL, Waldhausen JA. Effects of alterations in pulmonary vascular resistance on right ventricular function. *J Thorac Cardiovasc Surg*. 1967;54(6):886-894.
62. Ghio S, Gavazzi A, Campana C, et al. Independent and additive prognostic value of right ventricular systolic function and pulmonary artery pressure in patients with chronic heart failure. *J Am Coll Cardiol*. 2001;37(1):183-188.
63. Cingolani HE, Pérez NG, Cingolani OH, Ennis IL. The Anrep effect: 100 years later. *Am J Physiol Heart Circ Physiol*. 2013;304(2):H175-H182.
64. Brown SB, Raina A, Katz D, Szerlip M, Wiegers SE, Forfia PR. Longitudinal shortening accounts for the majority of right ventricular contraction and improves after pulmonary vasodilator therapy in normal subjects and patients with pulmonary arterial hypertension. *Chest*. 2011;140(1): 27-33.
65. Miller WL, Grill DE, Borlaug BA. Clinical features, hemodynamics, and outcomes of pulmonary hypertension due to chronic heart failure with reduced ejection fraction: pulmonary hypertension and heart failure. *JACC Heart Fail*. 2013; 1(4):290-299.
66. Bursi F, McNallan SM, Redfield MM, et al. Pulmonary pressures and death in heart failure: a community study. *J Am Coll Cardiol*. 2012;59(3): 222-231.
67. Melenovsky V, Hwang S, Lin G, Redfield MM, Borlaug BA. Right heart dysfunction in heart failure with preserved ejection fraction. *Eur Heart J*. 2014;35(48):3452-3462.
68. Mohammed SF, Hussain I, AbouEzzeddine OF, et al. Right ventricular function in heart failure with preserved ejection fraction: a community based study. *Circulation*. 2014;130(25): 2310-2320.
69. Dupont M, Mullens W, Skouri HN, et al. Prognostic role of pulmonary arterial capacitance in advanced heart failure. *Circ Heart Fail*. 2012;5(6): 778-785.
70. Alaeddini J, Uber PA, Park MH, Scott RL, Ventura HO, Mehra MR. Efficacy and safety of sildenafil in the evaluation of pulmonary hypertension in severe heart failure. *Am J Cardiol*. 2004; 94(11):1475-1477.
71. Guazzi M, Tumminello G, Di Marco F, Fiorentini C, Guazzi MD. The effects of phosphodiesterase-5 inhibition with sildenafil on pulmonary hemodynamics and diffusion capacity, exercise ventilatory efficiency, and oxygen uptake kinetics in chronic heart failure. *J Am Coll Cardiol*. 2004;44(12):2339-2348.
72. Lewis GD, Shah R, Shahzad K, et al. Sildenafil improves exercise capacity and quality of life in patients with systolic heart failure and secondary pulmonary hypertension. *Circulation*. 2007;116(14): 1555-1562.
73. Behling A, Rohde LE, Colombo FC, Goldraich LA, Stein R, Clausell N. Effects of 5′-phosphodiesterase four-week long inhibition with sildenafil in patients with chronic heart failure: a double-blind, placebo-controlled clinical trial. *J Card Fail*. 2008;14(3):189-197.
74. Guazzi M, Vicenzi M, Arena R, Guazzi MD. Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study. *Circulation*. 2011;124(2):164-174.
75. Redfield MM, Chen HH, Borlaug BA, et al;

RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA*. 2013;309(12):1268-1277.
76. Borlaug BA, Lewis GD, McNulty SE, et al. Effects of sildenafil on ventricular and vascular function in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2015;8(3):533-541.
77. Califf RM, Adams KF, McKenna WJ, et al. A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). *Am Heart J*. 1997;134(1):44-54.
78. Mulder P, Richard V, Derumeaux G, et al. Role of endogenous endothelin in chronic heart failure: effect of long-term treatment with an endothelin antagonist on survival, hemodynamics, and cardiac remodeling. *Circulation*. 1997;96(6):1976-1982.
79. Sütsch G, Kiowski W, Yan XW, et al. Short-term oral endothelin-receptor antagonist therapy in conventionally treated patients with symptomatic severe chronic heart failure. *Circulation*. 1998;98(21):2262-2268.
80. Packer M, McMurray J, Massie BM, et al. Clinical effects of endothelin receptor antagonism with bosentan in patients with severe chronic heart failure: results of a pilot study. *J Card Fail*. 2005;11(1):12-20.
81. Andersen MJ, Hwang SJ, Kane GC, et al. Enhanced pulmonary vasodilator reserve and abnormal right ventricular: pulmonary artery coupling in heart failure with preserved ejection fraction. *Circ Heart Fail*. 2015;8(3):542-550.
82. Abraham WT, Adams KF, Fonarow GC, et al; ADHERE Scientific Advisory Committee and Investigators; ADHERE Study Group. In-hospital mortality in patients with acute decompensated heart failure requiring intravenous vasoactive medications: an analysis from the Acute Decompensated Heart Failure National Registry (ADHERE). *J Am Coll Cardiol*. 2005;46(1):57-64.
83. Fawzy ME, Hegazy H, Shoukri M, El Shaer F, ElDali A, Al-Amri M. Long-term clinical and echocardiographic results after successful mitral balloon valvotomy and predictors of long-term outcome. *Eur Heart J*. 2005;26(16):1647-1652.
84. Fawzy ME, Hassan W, Stefadouros M, Moursi M, El Shaer F, Chaudhary MA. Prevalence and fate of severe pulmonary hypertension in 559 consecutive patients with severe rheumatic mitral stenosis undergoing mitral balloon valvotomy. *J Heart Valve Dis*. 2004;13(6):942-947.
85. Mubeen M, Singh AK, Agarwal SK, Pillai J, Kapoor S, Srivastava AK. Mitral valve replacement in severe pulmonary arterial hypertension. *Asian Cardiovasc Thorac Ann*. 2008;16(1):37-42.
86. Bishu K, Suri RM, Nkomo VT, et al. Prognostic impact of pulmonary artery systolic pressure in patients undergoing transcatheter aortic valve replacement for aortic stenosis. *Am J Cardiol*. 2014;114(10):1562-1567.
87. Patlolla B, Beygui R, Haddad F. Right-ventricular failure following left ventricle assist device implantation. *Curr Opin Cardiol*. 2013;28(2):223-233.
88. Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant*. 2014;33(6):555-564.
89. Mandarino WA, Morita S, Kormos RL, et al. Quantification of right ventricular shape changes after left ventricular assist device implantation. *ASAIO J*. 1992;38(3):M228-M231.
90. Moon MR, Castro LJ, DeAnda A, et al. Right ventricular dynamics during left ventricular assistance in closed-chest dogs. *Ann Thorac Surg*. 1993;56(1):54-66.
91. Farrar DJ, Compton PG, Hershon JJ, Fonger JD, Hill JD. Right heart interaction with the mechanically assisted left heart. *World J Surg*. 1985;9(1):89-102.
92. Farrar DJ. Ventricular interactions during mechanical circulatory support. *Semin Thorac Cardiovasc Surg*. 1994;6(3):163-168.
93. Raina A, Vaidya A, Gertz ZM, Susan Chambers, Forfia PR. Marked changes in right ventricular contractile pattern after cardiothoracic surgery: implications for post-surgical assessment of right ventricular function. *J Heart Lung Transplant*. 2013;32(8):777-783.
94. Houston BA, Kalathiya RJ, Maltais S, et al. Right Ventricular Adaptation to Afterload Worsens Up to 6 Months After LVAD Implantation But Improves Over Time. *J Heart Lung Transplant*. 2015;34(4):S63-S64.