Review Article

Right Ventricular Dysfunction and Failure in Chronic Pressure Overload

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Right ventricular (RV) dysfunction is the main cause of death in pulmonary arterial hypertension (PAH). Our understanding of the pathophysiology of RV dysfunction is limited but improving. Methods to better diagnose RV dysfunction earlier and treatments specifically designed to minimize or reverse the remodeling process are likely to improve outcomes. We review the current understanding of RV dysfunction in chronic pressure overload and introduce some novel insights based on recent investigations into pathophysiology, diagnosis, and treatment.

1. Introduction

Dysfunction of the right ventricle (RV) can occur in a number of clinical scenarios including pressure overload, cardiomyopathies, ischemic, congenital, or valvular heart disease, arrhythmias, and sepsis. Pressure overload can occur in an acute or chronic setting. Diagnosis is made on the compilation of data from the history and physical examination, electrocardiogram, chest X-ray, echocardiogram, and invasive hemodynamics. RV failure is associated almost universally with poor prognosis. Early recognition is essential to improve outcomes. Although pressure overload can occur with pulmonary valvular stenosis, the most common cause of pressure overload is pulmonary arterial hypertension (PAH). Recent advances, particularly in PAH management, have highlighted the importance of RV function and stimulated renewed interest in better understanding its adaptation to pressure overload. This is particularly evident over the past year, in which RV function has been reviewed several times [1, 2], as has echocardiographic methods of imaging the RV [3], RV function in cardiac and thoracic surgery [4–6], the mechanisms underlying RV failure in PH [7], and the treatment of acute right heart failure [8].

2. Chronic RV Pressure Overload

PAH is defined as a mean pulmonary artery pressure >25 mm Hg with a pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end-diastolic pressure ≤15 mm Hg [9]. Historically, long-term outcomes have been quite poor because of progressively increasing hypertension resulting in severe RV failure. But clinical outcomes have significantly improved with the recent advent of several pulmonary-specific vasodilators [10–13], such as prostanoids, endothelin receptor antagonists, and phosphodiesterase 5A (PDE5A) inhibitors. Median survival for patients with PAH without treatment is 2.8 years with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively [10]. With continuous prostanoid treatment, survival has improved 87-88%, 63–71%, and 56%, respectively [12, 14]. Similar results have been seen with the oral endothelin receptor antagonist bosentan (82–96% survival at 1 year; 67–89% 2-year survival) [15]. RV function is a critical determinant of patient outcomes in PAH and has recently been recognized as an important avenue for further research [16]. RV failure is the end result of PAH and the cause of at least 70% of all PAH deaths [10]. Unfortunately, identifying which patients will progress to RV

failure and at what time in the course of disease has been difficult.

3. Pathophysiology of RV Adaptation to Chronic Pressure Overload

One of the key features to RV adaptation to chronic pressure overload is hypertrophy. In general terms, this is felt to be due to increased wall stress due to increased pressure (Laplace's Law). Myocyte size increases via the synthesis of additional sarcomeres [7]. Extracellular matrix increases as well, with resultant increased fibrosis. At some point, adaptation is insufficient in the face of the pressure overload, resulting in dilation, decreased systolic and diastolic function, and frank RV failure. Unfortunately, this sequence of events is not understood well in the RV. There is a decrease in α-subtype myosin heavy chain relative to the β-subtype that is implicated in decreased systolic function [17, 18]. Actin expression is also altered in PAH, as might be the troponin complex [7]. Pressure overload causes alterations in β-adrenoreceptor and angiotensin type 1 receptor densities. As with LV failure, RV failure is associated with upregulation of the renin-angiotensin system. RV ischemia also has been documented in PAH indicating that oxygen supply-demand mismatch is likely implicated in the development of RV hypertrophy and failure [19] which may be due to decreased microvasculature recruitment or reduced vasodilatory capacity [7]. Upregulation of myocyte apoptosis in the pressure-overloaded RV also likely contributes to progressive RV dysfunction [7]. Mitochondrial nitric oxide synthase (mtNOS) is upregulated in the hypertrophied RV myocardium and is partially reversed by treatment with the PDE5A inhibitor, sildenafil [20]. These findings are in keeping with prior studies showing increases in PDE5 expression [21], the mitochondrial membrane potential [22], and glucose uptake [23] in RV tissue in patients with PAH and may represent a novel target for RV-specific therapeutic intervention [24].

Regional heterogeneity of RV remodeling and dysfunction has been observed in patients with PAH [25]. Hypertrophy is greatest in the RV outflow tract and worse in patients with decompensated RV function (Figure 1). Regional wall thickening, as a measure of regional function, is significantly decreased in the outflow tract (infundibulum) of patients regardless of RV functional status, with corresponding increased wall stress in this region. Initial reports from our group have suggested that alterations in regional RV structure and function, particularly in the outflow tract, precede overt hemodynamic RV decompensation, in that patients with less severe RV failure have selective outflow tract hypertrophy, whereas patients with severe RV failure have a generalized RV hypertrophy. These results need to be confirmed prospectively in patient cohorts in whom the progression of disease can be followed over time and treatments, but this asymmetrical hypertrophic response is consistent with an earlier study that found greater fiber shortening in the outflow tract compared with the RV sinus region and a sequential timing of contraction in the two regions [26]. Hypertrophy and dysfunction in the outflow tract may be an early sign of RV impending RV failure and suggests that a better understanding of RV remodeling on a regional level may greatly advance our knowledge of RV response to disease.

4. Identifying RV Dysfunction

Identifying RV dysfunction at less severe stages, which would allow for earlier intervention and potentially better long-term results, has been limited largely due to complex RV three-dimensional geometry that defies the assumption of a simple ellipsoid, complex LV/septum interactions, and lack of accepted approaches to assess regional and organ-level RV function. Current markers of RV failure that have been associated with poor outcomes only recognize end-stage disease. There have been several recent approaches to better identify RV dysfunction.

The clinically accepted gold standard for identifying RV dysfunction and understanding physiology in the pressure-overloaded state remains invasive hemodynamics [1]. Right atrial pressure, cardiac output, and mean pulmonary arterial pressure all have been prognostic of outcomes in PAH [10]. Measurement of hemodynamics with exercise can further identify PAH not apparent at rest, distinguish from LV diastolic dysfunction, and aid in prognosis (failure to increase cardiac output with exercise) [1]. Pressure-volume loops of RV function in chronic PAH can provide additional information beyond standard hemodynamics. For example, prostacyclin has been shown to improve ventricular-vascular coupling (ratio of contractility as defined by the end-systolic pressure-volume relationship, Ees, to afterload as defined by pulmonary arterial elastance, which itself is the ratio of end-systolic pressure to stroke volume; Figure 2) [27]. This methodology has been used to show enhanced contractility (end-systolic pressure-volume relationship, Ees) despite lower cardiac output and ventricular-vascular decoupling (lower ratio of Ees to pulmonary arterial elastance, Ea) in PAH [28]. Measures of hemodynamics that take into consideration the pulsatility of pulmonary blood flow further offer an opportunity to better understand the hydraulic load that the RV encounters. Increased vasculature stiffness results in increased fluid wave reflections and an increased RV pump workload. While pulmonary vascular resistance (transpulmonary gradient divided by cardiac output) is the clinical standard measurement of pulmonary vascular load, this only provides information on the static load. However, $1/3 - 1/2$ of the pulmonary load (hydraulic power) is due to the pulsatile nature of blood flow [1]. Load in a pulsatile flow system is better characterized by input impedance. One recent study of pulmonary vascular input impedance in 49 pediatric patients with PAH predicted clinical outcomes at one year better than pulmonary vascular resistance [29]. Such measures of pulsatile load and ventricular-vascular coupling may help explain when and how the RV fails [30], leading to improved diagnosis and more individualized treatment [31].
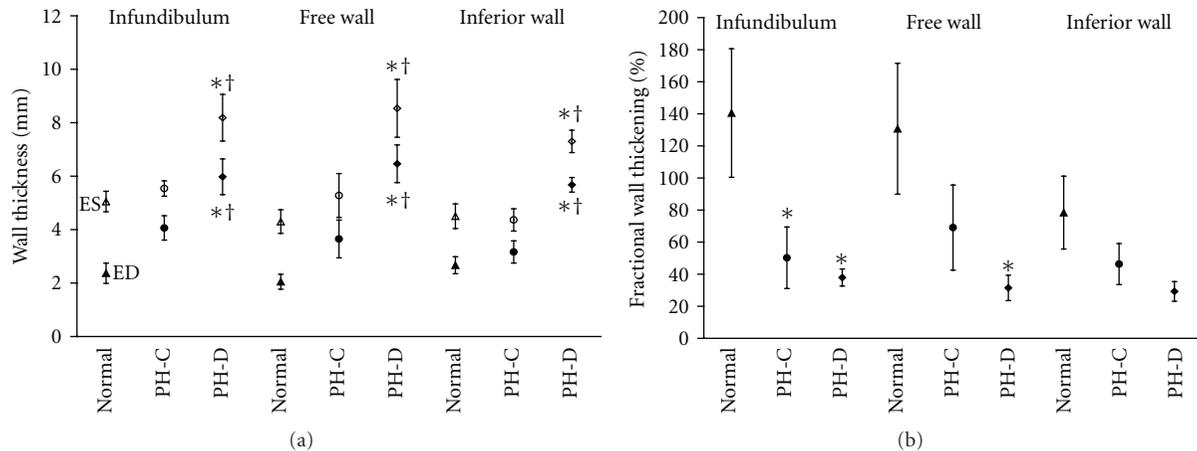
FIGURE 1: Regional heterogeneity of RV remodeling and dysfunction observed in patients with pulmonary hypertension. Patients were divided into one of three groups based upon hemodynamic parameters: Normal (normal pulmonary artery [PA] pressure, defined as mean PA pressure ≤ 25 mmHg), PH-C (PH with hemodynamically compensated RV function, defined as mean PA pressure >25 mmHg and right atrial [RA] pressure <10 mmHg), and PH-D (PH with hemodynamically decompensated RV function, defined as mean PA pressure ≥ 25 mmHg, and RA pressure ≥ 10 mmHg). (a) Regional RV wall thickness in end diastole (ED, filled symbols) and end systole (ES, open symbols). (b) Corresponding fractional wall thickening. $*P < 0.05$ PH-C versus Normal or PH-D versus Normal; $†P < 0.05$ PH-D versus PH-C, from [25].

Echocardiography is a standard clinical method to assess the RV in PAH. It has, as its major advantage, its noninvasive nature allowing sequential studies over time and good visualization of the major RV structures and functions in a dynamic fashion. Although echocardiographic assessment of pulmonary artery pressure can be made from the tricuspid regurgitant jet, treatment decisions based on PAH hemodynamics need to be confirmed invasively. Additionally, the ability to estimate pulmonary artery pressure from the tricuspid regurgitant jet is quite useful, although for treatment decisions in PAH hemodynamics must be confirmed invasively. Fractional area change (FAC), as a surrogate of ejection fraction, is calculated by analyzing the difference in the cross-sectional area of the RV in systole and diastole and has prognostic value in small studies, as does RV enlargement, tricuspid regurgitations, pericardial effusion, and the Tei (myocardial performance) index [9]. Newer techniques include tissue Doppler imaging (TDI) and speckle tracking. Peak systolic strain of the RV free wall by TDI is reduced in PH patients, and this measure correlates with transpulmonary gradient, pulmonary vascular resistance, and cardiac index [32]. RV free wall peak systolic strain has been found to decrease with PH and decreases further with RV decompensation [33]. TDI of the RV has also demonstrated good correlation with cardiac magnetic resonance (CMR) derived RV ejection fraction [34]. Speckle tracking has also been used to quantify RV myocardial strain and may be a valuable method to detect preclinical disease because it detects minor changes not easily quantified by TDI. For example, speckle tracking RV myocardial strain patterns have identified abnormal RV contraction in systemic sclerosis patients with normal pulmonary pressures, even when other markers such as tricuspid annular plane systolic excursion were unchanged from normal [35–37]. A reliable method to identify

pre-clinical RV dysfunction would be an important advance in RV imaging. Three-dimensional echocardiography has been validated as a method to assess RV volumes and has been used to evaluate RV function [38–40]. Limitations of echocardiography include limited acoustic windows for imaging the complex three-dimensional structure of the RV.

CMR has been useful for anatomical assessment of the RV and more recently functional assessment as well. Two recent reviews of CMR in PAH have recently been published [41, 42]. RV volume, mass, and stroke index measures by CMR predicted 1-year survival in 64 PAH patients [43]. Measures of PA stiffness by CMR (pulsatility, compliance, capacitance, distensibility, elastic modulus, and the pressure-independent stiffness index) have been reported to be a sensitive measure of early PAH [44]. Blood flow imaging by CMR has been used to detect vortices of blood flow in the main pulmonary artery of patients with PAH [45]. However, many, if not most, measures of RV function by CMR are not yet standardized.

Computed tomography (CT) also can be useful to assess RV structure and function due to its high spatial resolution, accessibility, and quick scan times, though it is limited by radiation and contrast exposure [46–48]. CT has been used to identify regionally heterogeneous RV remodeling and dysfunction in pulmonary hypertension [25]. This is consistent with findings of a study by CMR and echocardiography that found greater fiber shortening in the outflow tract compared with the RV sinus region [26].

5. Treatment of Pressure Overload-Induced RV Dysfunction

Clinical trials data are still quite limited on the effect of PAH-specific treatment on RV function as are data on any specific

(a)

(b)

(c)
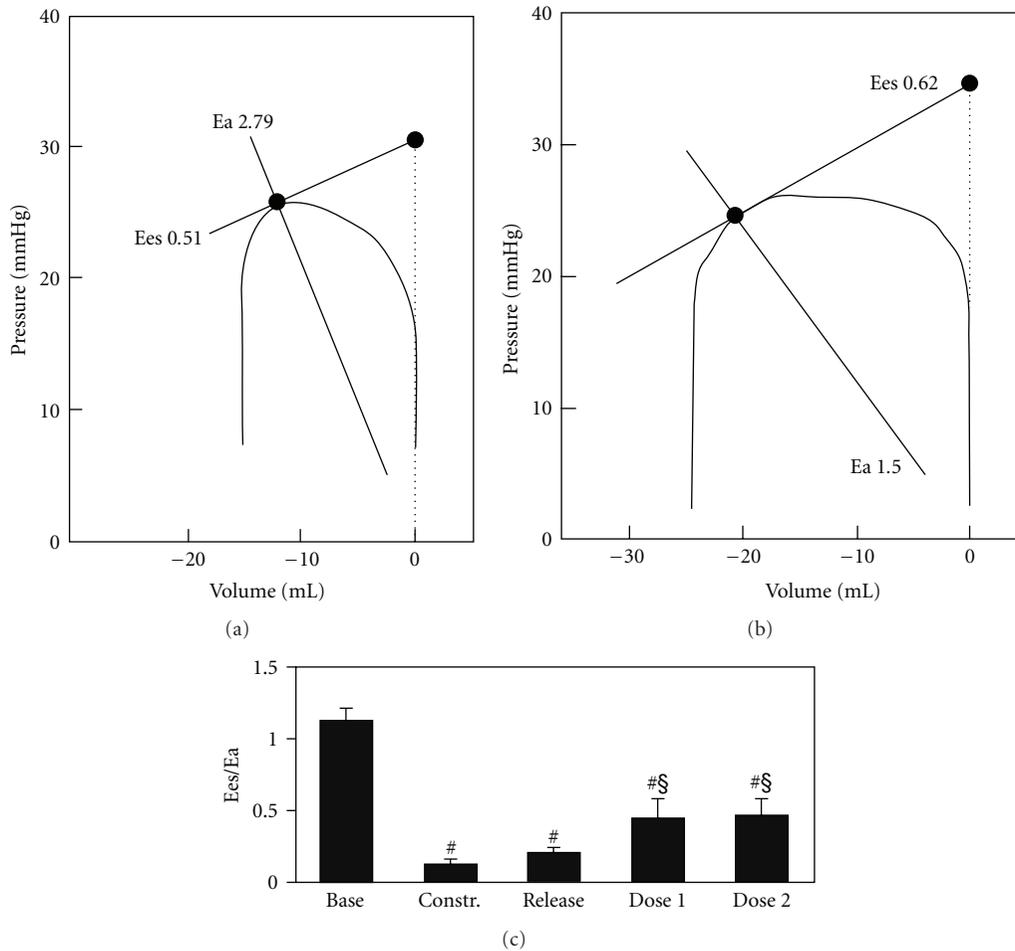
FIGURE 2: Example of ventricular-vascular coupling analysis. Systolic portions of the RV pressure-volume curves showing end-systolic elastance (Ees) and arterial elastance (Ea) lines. Ventricular-vascular coupling (Ees/Ea) is improved with prostacyclin due to a decrease in arterial elastance (Ea) in a dog with acute RV failure induced by transient pulmonary artery constriction. (a) Prior to prostacyclin infusion. (b) After prostacyclin infusion. (c) Ventricular-vascular coupling efficiency (Ees/Ea) at baseline, during pulmonary artery constriction (Constr.), after pulmonary artery release, and during prostacyclin infusion at 2 doses ($n = 7$; values are means + standard error). $^{\#}P < 0.05$ compared with baseline; $^{§}P < 0.05$ compared with release, adapted from [27].

therapy for RV dysfunction. Regression of RV hypertrophy has been seen after 1 year of treatment with high-dose calcium channel blocker [49]. Prostacyclin treatment has been associated with modest RV reverse remodeling, specifically reversing some dilation and sphericity, as well as improved RV stroke volume [50, 51]. In a small retrospective study, the endothelin receptor antagonist bosentan resulted in improvements in invasive hemodynamics, functional status, and a trend in improvement in RV stroke volume, but no significant change in RV volume or ejection fraction [52]. The PDE5A inhibitor sildenafil increases RV contractility in isolated rat heart preparations and individual cardiomyocytes [21]. A least one ongoing multicenter PAH treatment study (with bosentan) is currently evaluating RV response to treatment with serial cardiac MRI with results hopefully to be reported within the next year [53].

There are some unique therapies in early-stage investigation that have been reported specifically to improve RV function in the pressure-overloaded state. A plant extract improved RV function in a rat model of PAH with severe RV failure [54]. A tissue-engineered skeletal myoblast sheet improved RV diastolic function, minimized fibrosis, and increased capillary density in a rat model of PAH [55]. There has been a suggested role for RV pacing as cardiac resynchronization therapy in PAH as RV dyssynchronous contraction has been observed to correlate with disease severity [56–58].

6. Conclusion

Although our knowledge of RV dysfunction in chronic pressure overload is progressing, there is still much that needs to be understood. Particular attention should be paid to the impact of PAH on ventricular-vascular interactions and how pathophysiologic derangements result in organ level dysfunction. Regional assessments of the RV may provide an avenue for better understanding mechanisms of RV

dysfunction and earlier diagnosis because nonhomogeneous RV adaptation appears to be an early marker of impending RV failure in PAH. Importantly, novel therapies to specifically improve RV remodeling and dysfunction in chronic pressure overload are greatly needed.

Disclosures

Acknowlegments

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