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Diagnosing And Treating The Failing Right Heart

John J. Ryan¹ and Ryan J. Tedford²

¹Division of Cardiovascular Medicine, Department of Medicine, University of Utah, Salt Lake City, UT, United States

²Division of Cardiology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD United States

Abstract

Purpose of review—Right ventricular failure (RVF) is associated with significant morbidity and mortality. There is an increasing interest in proper assessment of right ventricle (RV) function as well as understanding mechanisms behind RVF.

Recent findings—Within this manuscript, we discuss the metabolic changes that occur in the RV that occur in response to RVF- in particular, a shift towards glycolysis and increased glutaminolysis. We will detail the advances made in non-invasive imaging in assessing the function of the RV and review the methods to assess right ventricle-pulmonary artery coupling. We lastly investigate the role of new treatment options in the failing RV, such as β -blocker therapy.

Summary—RVF is a complicated entity. Although some inferences on RV function and treatment can be made from LV, the RV has unique features, anatomically, metabolically and embryologically, which requires dedicated RV-directed research.

Keywords

Right Ventricle; Right Heart Failure; Ventricular-Vascular Coupling; Warburg effect; glycolysis; Randle's cycle

Introduction

For many years, the right heart and its potential role in disease had been largely ignored. Observations from patients with Fontan circulation who could live for periods of time without heart failure symptoms contributed to the belief that the right heart was essentially nothing more than a passive conduit. These patients in fact did do well, until the systemic ventricle began to fail or pulmonary hypertension (PH) developed – both situations in which RV afterload is increased. It is now evident that the function of the right heart is directly related to outcomes in many disease states including pulmonary arterial hypertension (PAH)

Address for correspondence: John J. Ryan MB BCH, FAHA, FACC. Assistant Professor, Division of Cardiovascular Medicine, University of Utah Health Science Center 30 North 1900 East, Room 4A100 Salt Lake City, UT 84132 john.ryan@hsc.utah.edu; (P): 801-585-2341; (F): 801-587-5874.

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[1,2], heart failure with reduced [3,4] and preserved [5,6] ejection fraction, and heart failure after implantation of left ventricular assist devices (LVAD).[7] The International Right Heart Foundation Working Group recently proposed a comprehensive definition of right heart failure: “a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory 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.”[8] Although the RV is a very important part of the right heart system (and the main focus of this review), failure of any component of the circulation from the systemic veins up to the pulmonary capillaries can result in right heart failure symptoms.

The Normal Right Ventricle

The normal RV is a thin-walled crescent shaped structure that is composed of the RV free wall, interventricular septum, and RV outflow tract. Although it is a distinct embryologic structure from the left ventricle (LV), the interventricular septum has shared fibers with the LV. [9] As a consequence of these shared fibers, the LV accounts for as much as 30-50% of RV contractile function. [10] The septum itself, via its efficient longitudinal/twisting contraction, contributes most to overall RV function as compared with the transverse motion of the RV free wall.[9] In fact, it has been estimated that longitudinal shortening accounts for almost 80% of RV function in normal physiologic states.[11]

Etiology of Right Ventricular Failure

The etiologies of RV failure (RVF) are many and varied but LV failure remains the leading cause (Table 1). The same factors that lead to left-sided dysfunction can also impact the RV, causing intrinsic RV dysfunction. RV contractility may further be reduced because the RV depends on the LV for a substantial portion of its function as noted above.

The RV normally ejects blood into a low afterload, highly compliant arterial circuit. When afterload is increased, especially acutely, a marked reduction in RV function can occur.[12] Elevated left-sided filling pressures not only increase pulmonary pressure passively but also lower vascular compliance, thereby augmenting pulsatile RV afterload.[13] Over time, LV failure may also precipitate pulmonary arterial vasoconstriction and/or remodeling further elevating afterload. In some cases of chronic or slowly progressive elevations in afterload, the RV is able to compensate relatively well, as is the case with Eisenmenger's syndrome. [14] In others, it is not. Continued efforts are underway to diagnose and predict the development of RVF secondary to increased left-sided filling pressures, most particularly as it complicates implantation of LVADs. With increased understanding of cardiomyocyte dysfunction in PH and RVF, it is worth reviewing the advances made in the past year on molecular signaling in the failing RV.

Molecular Changes in the Right Ventricle

There is increasing appreciation and acceptance of the metabolic changes that develop in the failing RV[15], and has been particularly well studied in PAH-associated RVF. In RVF, a metabolic shift from mitochondrial oxidative phosphorylation to cytoplasmic glycolysis has been identified as the RV undergoes hypertrophy, as evidenced by increased uptake of

Fluorodeoxyglucose-Positron emission tomography (FDG- PET) scan[16] and by direct measurement of metabolism in an RV working heart model.[17] This increase in glycolysis is accompanied by a decrease in fatty acid oxidation, referred to as the Warburg effect, a phenomenon that has traditionally been used in discussing metabolism of cancer cells[18], and is mediated by hyperpolarized mitochondrial membrane potential. In PAH, the accompanying increase in RV afterload creates an ischemic RV, due at least in part to compromised right coronary artery (RCA) blood flow.[19] Furthermore, there is observed capillary rarefaction in the RV of patients with PAH, most particularly with scleroderma-associated PAH.[17]

In the setting of an ischemic myocardium, mitochondria-dependent apoptosis is suppressed and there is decreased production of mitochondria-derived reactive oxygen species (mROS), potentially to minimize stress in a hypertrophying myocardium.[20] While the RV remains compensated, there is an increase in Hypoxia-Inducible Factor 1 α (HIF1 α), which may promote angiogenesis to counteract for the increased O₂ demands of a hypertrophied RV. When the RV becomes decompensated, there is an increase in mROS, a decrease in HIF1 α and a decrease in glucose oxidation. In this setting, patients with PAH enter into a syndrome of pronounced RVF, especially as the decrease in HIF1 α is accompanied by decreased angiogenesis and exacerbation of ischemia in the RV.[20]

Additive to the cancer phenotype is the recent observation that there is an increase in glutaminolysis within the RV of patients and animals with PAH.[21] Glutaminolysis is the metabolism of glutamine, which in cancer allows for rapid cell growth without apoptosis. [22] In RVH, capillary rarefaction and RV ischemia activate the proto-oncogene *cMyc*, which increases glutamine uptake and in turn increases production of α -ketoglutarate (α -KG). α -KG then enters Krebs cycle producing malate. This Krebs cycle-derived malate then generates cytosolic pyruvate, which in turn is converted by lactate dehydrogenase A to lactate. In the setting of increased glutaminolysis, this is accompanied by inhibition of glucose oxidation. This maladaptive pathway has the potential to be therapeutically manipulated by inhibitors of glutaminolysis, which would then optimize cellular metabolism in the failing RV by increasing glucose oxidation.

Peroxisome proliferator-activated receptor-gamma coactivator 1 α (PGC-1 α) governs a large numbers of genes that regulate mitochondrial function[23] and has been shown to be downregulated in the failing RV.[24] This decreased expression of RV PGC-1 α results in a loss of mitochondrial protein and oxidative capacity. In fact, not only is this decrease in PGC-1 α associated with decreased mitochondrial number, but also the mitochondria become hyperpolarized, abnormally shaped and have a reduced ADP-stimulated (state 3) rate for complex I.[24] These structural and functional abnormalities of the RV mitochondria provide credence to the theory of mitochondrially-mediated metabolic abnormalities in the failing RV and offer therapeutic potential in the form of metabolic modulators such as the pyruvate dehydrogenase kinase inhibitor, dichloroacetate (DCA), which is currently the study of clinical trials in PAH.[25]

There is ongoing debate and controversy regarding the sequence of events in the RV, namely the timely of mitochondrial dysfunction as it relates to the development of RVF[26],

but it is apparent that the glycolytic shift that occurs in the RV is a maladaptive response and can ultimately contribute to the “burning out” of the RV.[26] Furthermore, the loss of the angiogenic program contributes to the loss of capillaries which contributes to ischemia and the loss of mitochondrial hyperpolarization facilitates myocardial apoptosis, which can potentially thin out the RV and contribute to RV decompensation and failure.[20]

Assessment of Right Ventricular Function

Non-invasive Measures

Accurate and comprehensive assessment of RV function remains a challenge. The RV can be technically difficult to image and the afterload dependence of the RV can also lead to misleading interpretations of intrinsic RV function. Noninvasively, echocardiography and magnetic resonance imaging (MRI) are the most often used clinical tools. Because the majority of RV function occurs via longitudinal shortening, tricuspid annular systolic plane excursion (TAPSE) is an attractive candidate to assess RV function. TAPSE has been shown to correlate with outcomes in multiple cohorts of patients with PAH[2,27] and LV failure.[4-6] However, other data suggests changes in TAPSE may not be reliable marker of disease progression[28] and may also not represent global RV function in congenital heart disease[29] or after cardiac surgery.[30] After cardiac surgery, longitudinal shortening is depressed – from acquired septal dysfunction[31] and/or loss of pericardial constraint[32] - and the RV becomes more dependent on transverse shortening by the RV free wall.[30] Despite the decline in longitudinal function, RV fraction area change (RVFAC) and RV ejection fraction (RVEF) may be preserved, especially if afterload is low.[30,33] Although RVEF is difficult to interpret by conventional echocardiography, RVFAC and TAPSE correlated well with MRI derived RVEF in a recent study of patients with PH[34].

Strain imaging is increasingly being utilized to assess RV function. Strain is likely a composite measure of RV loading and dysfunction and as such abnormal strain patterns likely develop from microvascular ischemia (Table 1) as well as myocardial disarray from distension of the RV. Sachdev studied RV longitudinal strain in 80 patients with PAH and discovered that worse RV strain was associated with disease progression, higher diuretic use, and mortality.[35] Although risk scores have traditionally focused on clinical parameters[36] to predict RVF after LVAD implantation, more recent efforts have concentrated on using echocardiographic strain assessments of the RV to risk stratify patients. In this setting, RV strain patterns have been shown to add incremental benefit on top of clinical risk scores.[37] Free-wall RV longitudinal strain also best predicts clinical outcomes in patients referred for heart transplantation, when compared with N-terminal pro-BNP, global strain patterns, left ventricular ejection fraction and other echocardiographic parameters.[38] Additionally, in Group 1, 3 and 4 PH, RV longitudinal peak systolic strain as assessed and measured by speckle-tracking echocardiography can predict survival even when adjusted for invasive hemodynamics and RV strain provides incremental prognostic value over conventional echocardiographic and clinical variables.[39] Serial assessments and changes in strain rates in response to treatment may also have prognostic value[40], although reliance solely on longitudinal strain may not account for changes in the contractile patterns late in disease or after surgery.[41] Freed recently demonstrated RV longitudinal

strain measured by echocardiogram correlated with MRI-derived RVEF but only correlated moderately with MRI-derived strain.[42] This later finding suggests strain measures may not be interchangeable among imaging modalities. Routine assessment of RV strain in patients with risk factors and/or diseases that can predispose to RV failure may become a necessary skill to develop in echocardiography laboratories over the next few years.

Cardiac MRI has become the gold standard for noninvasive assessment of RV function and is then most accurate method for determining RV mass, volume, and EF.[43] Van de Veerdonk and colleagues found a change in RVEF, assessed by MRI, was the variable most predictive of outcome in patients receiving PAH-specific therapy.[1] In another study by the same group, increases in RV size and declining RVEF predicted clinical worsening in patients with idiopathic PAH.[44] Investigators from the multicenter EURO-MR study have shown on-treatment changes in RV (especially RVEF) and LV parameters predict improvement in functional capacity.[45] As in PAH, lower RVEF portends a worse outcome in left heart failure.[3,46]

Invasive Hemodynamics

Hemodynamic variables obtain via right heart catheterization may aid in assessing right heart function. Elevated right atrial pressure (RAP) and low cardiac index are associated with worse survival in historical and more modern cohorts of PAH.[47,48] However, one must remember than factors other than RV dysfunction may contribute to elevations in RAP including pericardial constraint .[49] Elevation in pulmonary vascular resistance (PVR) (>3 Wood units) is associated with poor prognosis in left heart disease [50,51] and PAH.[48] More recently, pulmonary vascular compliance (estimated as stroke volume/pulmonary pulse pressure) has shown prognostic value in PAH [52] as well as left heart failure.[53-55] In left heart failure, compliance appears more predictive than PVR, because it incorporates the effect of pulsatile loading caused by elevated left side filling pressures.[13,53] Despite their prognostic value, both PVR and compliance are measures of afterload and do not directly reflect RV function.

Measures of Right Ventricular-Pulmonary Arterial Coupling

The gold standard for assessment of ventricular function and the effect of afterload is through the relation of ventricular pressure and volume. This type of analysis has been extensively performed in the LV, but the same principles also hold true for the RV. [56,57] By varying preload or afterload, a family of PV loops can be created, and the maximal ratio of pressure to volume ($P/[V-V_0]$, where V_0 is the volume-intercept) can be determined for each loop. As opposed to the LV, the normal RV pressure-volume (PV) loop is triangular in shape (Figure 1A) with pressure declining throughout ejection - indicative of the low impedance vascular system. Therefore, this maximal ratio of pressure and volume may not occur near endsystole, making PV assessment more difficult. However, the shape of the RV PV loop changes to more of a square shape (similar to the LV) in mild PH (Figure 1B) or even a trapezoidal shape in more severe PH (Figure 1C), with pressure continuing to rise throughout ejection[58]. In the latter two cases, the maximal ratio of pressure and volume will occur near end-systole as it does in the LV. The end-systolic pressure-volume relationship (ESPVR) can then be determined by connecting the end-systolic pressure (ESP)

points of each PV loop, the slope of which is the endsystolic elastance (Ees) - a relatively load-independent measure of contractility. By comparison, TAPSE, RVFAC, and RVEF are all load-dependent, and therefore do not directly measure intrinsic RV contractility.

Afterload may be estimated via the PV loop as the effective arterial elastance (Ea) – ESP divided by the stroke volume (SV). This ‘lumped’ parameter of afterload takes into account both resistive and pulsatile components and more completely describes total RV afterload than PVR alone. The ratio of these two elastances (Ees/Ea) can then be used to illustrate ventricular-vascular coupling. Measures of coupling are particularly attractive because they may help identify sub-clinical right heart failure. Impaired RV-PA coupling in systemic sclerosis-associated PAH compared with idiopathic PAH was recently shown via this technique when other imaging and hemodynamic variables failed to discriminate between the two groups.[58]

Although certainly feasible, these types of invasive measures require specialized equipment and significant expertise, and are not practical for routine clinical use. Therefore, less invasive ways to measure RV-PA coupling are currently being sought. One of these approaches uses a single, steady-state PV loop to estimate Ees, negating the need for load variation and multi-beat measures (so-called ‘single beat’ methods). First proposed by Brimiouille for the RV[59], one technique involves fitting a sine wave to the isovolumic portions of the RV pressure tracing to determine Pmax (Figure 2A), the theoretical maximal pressure the RV could generate if ejecting into infinite load. Thus, a second point (Pmax, end-diastolic volume) along the ESPVR is determined and Ees can be calculated (Figure 2B). Although good correlation was found between estimated and actual Pmax in normotensive dogs, the technique was not sensitive to inotropic induced changes in contractility[60] and was not predictive of outcome in a recent human study.[61] A second, even simpler estimation of Ees, assumes the volume intercept of the ESPVR is zero ($V_0=0$). In this case, Ees could be estimated as the ratio of ESP/end-systolic volume (ESV), and the ratio of elastances as SV/ESV [62]. Recently, a study by Vanderpool and colleagues, found SV/ESV was a predictor of survival in 50 patients with PAH[61]. The $V_0=0$ approach does have limitations however as it appear to underestimate Ees[63]. Additionally, V_0 can be highly variable depending on the contractile state of the RV[58], and therefore it is unlikely one can assume $V_0=0$. It is also important to remember that RVEF is directly related to Ees/Ea only if it is assumed that $V_0=0$ [64], and therefore is not a direct measure RV-PA coupling.

Given the limitations with direct measures of coupling, yet its importance in our understanding of the RV, other indirect measures of coupling have been explored. Combining noninvasive measures of contractile function and afterload into single parameters has shown prognostic promise in left heart failure[4] and predicted RV failure after LVAD implantation.[65] Using a pig model of PAH, Guihaire and colleagues recently showed that RV contractile reserve - measured by change in SV index, dP/dt max and Ees - were strongly related to resting RV-PA coupling.[66] Sharma reported RV contractile reserve limitation in 18 PAH patients, including those with “normal” resting function. In this group, lack of RV reserve correlated linearly with exercise capacity.[67] The idea that RV reserve may be predictive of resting coupling is intriguing because RV reserve (or lack thereof) has been predictive of prognosis in several recent PAH studies.[68,69] The

relationship of RV reserve to resting coupling and its use as a clinical tool warrants further investigation.

Management of Right Ventricular Failure

The optimum management of RV failure remains elusive, especially when it comes to the choice of inotropic agent to support the decompensated RV. In a recent study of PAH providers, there was considerable disagreement as to the first line inotrope in patients with PAH-related RVF with no standardized practice or globally accepted guidelines currently available for RVF.[70] Animal models of PAH provide some insight to support claims that inotropy in RVF (secondary to PAH) is best achieved with dobutamine due to improved coupling to adenylyl cyclase.[71] The potency of inotropes in the RV Langendorff model (in descending order) is: dobutamine = isoproterenol > dopamine > phenylephrine. Additionally, the superiority of dobutamine over dopamine may reflect the fact that dopamine relies heavily on Dopamine-1 receptor signaling, which is impaired in RV hypertrophy.[71]

Admission to an intensive care unit for RVF and consequent inotropic support has an inpatient mortality rate of over 40%.[72] In this setting, and with the absence of standardized protocols, there has been some interest in developing mechanical circulatory support targeting the RV.[73] To this end, the RECOVER Right Study is ongoing[74] in patients who developed RVF within 48 hours after implantation of a LVAD, or patients in post-cardiotomy shock or patients with post- acute myocardial infarction (AMI) shock. The results of this study will provide insight into the ability to unload the RV.

Although there is downregulation and desensitization of adrenergic (β 1- and α 1- adrenoreceptors) receptors in RVF, there is increasing interest in the feasibility of the use of β -blocker in chronic RVF (likely not acute RVF, akin to the practice in left ventricular systolic dysfunction). Carvedilol can reverse established RVF in two different rat models of PAH and the improvement in RV function is associated with improved capillary density and reduced hypertrophy of the myocardium.[75] Additionally, bisoprolol has been shown to delay progression toward RVF in animal model of PAH, and can, at least in part, preserve RV systolic and diastolic function.[76] Of note, genes encoding proteins involved in the mitochondrial dysfunction pathway are upregulated in PAH animals treated with carvedilol and protein ubiquitination pathways and genes encoding proteins involved in cardiac hypertrophy are downregulated in the RV by carvedilol.[77] When formally studied in humans with PAH, β - blockers are found to at least be safe. However, although no adverse events have been identified[78], no therapeutic clinical benefit have yet been observed either[79], so this will remain an area of investigation over the coming years as our efforts to modulate RV metabolism continue.

Conclusion

The diagnosis and treatment of the RVF continues to be challenging. As our understanding of molecular mechanisms evolve, we should be able to offer more therapeutic options of this final common pathway. However, whether the therapeutic targets will be on the

neuroendocrine system, or metabolic modulators remains to be seen and will be dependent on insight offered by cellular studies as well as through intricate hemodynamics.

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Key points

- Comprehensive assessment of RV function is difficult as it requires consideration of both RV contractility and afterload (RV-PA coupling).
- RV contractile reserve is prognostic in pulmonary hypertension and may identify patients with uncoupling at rest.
- RV failure has a very poor prognosis and no standardized treatment options are available.
- RV failure is accompanied by increased glycolysis, decreased glucose oxidation and increased glutaminolysis- and these abnormalities in metabolism are mediated through mitochondrial dysfunction.

Figure 1.

Examples of human right ventricular pressure-volume loops A) under normal loading conditions B) in mild pulmonary hypertension C) in more severe pulmonary hypertension. For B) and C), pressure rises throughout ejection and peaks near end-systole.

Figure 2.

Single-beat method of calculating end-systolic elastance (Ees): A) Sine wave is fit to the isovolumetric portions of a high-fidelity RV pressure tracing to determine Pmax. B) End-systolic elastance (slope of the grey dotted line) can be determined by the two points (Pmax, end-diastolic volume) and (end-systolic pressure, end-systolic volume).

Table 1

Etiology of Right Ventricular Failure

Increased afterload	Pulmonary Hypertension, Group 1-5. Increased left ventricular end-diastolic pressure. Mitral valve disease. Hypoxic pulmonary vasoconstriction. Pulmonary thrombo-embolus, acute or chronic. Pulmonary embolus (septic, amniotic, fat, air, injectate, other). Pulmonary valve stenosis. Right ventricular outflow tract obstruction. Vaso-occlusive sickle cell crisis. Mechanical ventilation.
Decreased preload	Hypovolemia. Systemic vasodilatory shock (anaphylaxis, extensive burn injury, sepsis, other). Tamponade. Constrictive pericarditis. Superior vena cava syndrome. Tricuspid stenosis.
Right ventricular myocardial abnormality	Right ventricular infarction. Infiltrative and restrictive cardiomyopathy. Arrhythmogenic right ventricular dysplasia. Cardiomyopathy, in particular left ventricular systolic dysfunction. Right ventricular ischemia in setting of right ventricular pressure overload. Microvascular diseases and capillary rarefaction.