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Novel Therapeutic Approaches to Preserve the Right Ventricle

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Abstract

The right ventricle (RV) is increasingly recognized for its role in heart disease. In fact, RV function is a strong predictor of outcome in patients with cardiovascular disease. Although the focus in heart failure has been on the left ventricle (LV) recently the spotlight has been shifting to include the RV. The right and left ventricles have different embryological origins and respond differently to stressors and to therapies.

Newer therapies targeting the RV have been investigated in an attempt to improve right ventricular adaptation to cardiovascular diseases. In this review, we summarize the differences between the right and left ventricles and focus on novel therapies that target the RV.

Keywords

Right ventricle; heart failure; pulmonary hypertension; right ventricle hypertrophy

Introduction

In heart failure, the LV has been the focus of extensive investigations; similarly, in pulmonary hypertension (PH), the emphasis has been on the pulmonary vasculature. However, RV dysfunction is an independent predictor of negative outcomes in both diseases[1, 2], and there has been increasing interest in better understanding the role of the RV in the pathophysiology of cardiopulmonary disease and in developing therapies to target RV performance. Here we review the differences between the RV and LV, the RV response to pressure overload, and the different RV targeted therapies being investigated.

Right Ventricular Embryology

The first solid organ to form during development is the vertebrate heart[3]. The four key stages in cardiac morphogenesis include tubular heart formation, cardiac looping, chamber formation and complete septation with development of coronary circulation[4]. Early on, the linear heart tube begins as a flat sheet of mesodermal cells. The cardiac progenitor cells originating from the anterior splanchnic mesoderm migrate to an anterior lateral position to form bilateral heart primordia (the primary heart field). The primary heart tube forms as a

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result of cranial to caudal fusion of the paired heart primordia. The cranial regions become the ventricles and the caudal regions give rise to the atria. More recently, it was recognized that a second group of cells derived from pharyngeal mesoderm (the secondary heart field) are important source of cardiac stem cells for later development. In fact, the cardiac crescent (primary heart field) gives rise to the LV; whereas the rest of the heart, the RV, outflow tract and atria derive from the secondary heart field[5]. As such the RV originates from a different embryological source than the LV.

Differences Between the Right and Left Ventricles

The right and left ventricles are quite different in their physiology and their adaptation to pathological conditions. In utero, both RV and LV wall thickness increases in parallel as the RV is pumping against a high resistance pulmonary bed[6]. However, at birth, as the pulmonary vascular bed remodels and becomes a low-pressure low-resistance bed, the RV becomes thin walled about one third the thickness of the LV. In addition to its muscle mass being about one-sixth that of the left ventricle, the RV has a distinct crescent shape compared to the ellipsoidal, concentric shape of the LV and its mechanism of contraction is different from the LV. These characteristics allow the RV to adapt to conditions of volume overload and the LV to conditions of pressure overload. In fact, while the LV compensates to acute and chronic increases in pressure afterload, the RV does not.

Right Ventricular Failure

RV dysfunction and subsequent failure results from three main mechanisms: (i) intrinsic myocardial disease, (ii) volume overload and (iii) pressure overload. The most common cause of RV dysfunction is LV dysfunction and failure that can lead to pressure overload and pulmonary venous hypertension. The RV is not suited to sustain pressure overload and the mechanisms that help the RV adapt to the increase in pulmonary pressures ultimately lead to a maladaptive remodeling with RV dilation and eventual failure. In acute conditions such as massive pulmonary embolism, acute RV pressure overload can lead to RV failure and cardiovascular collapse. However, in conditions of chronic pressure overload, RV hypertrophy (RVH) develops in an attempt to compensate for the increased afterload and to maintain cardiac output. In conditions of pressure overload resulting from congenital heart diseases, RVH is concentric with preserved function. This adaptive mechanism has been hypothesized to be due to persistent expression of fetal genes. In adulthood, RV pressure overload leads to RV myocardial hypertophy and luminal dilatation to maintain stroke volume. This compensatory mechanism leads to a mismatch between myocardial blood supply and increased oxygen demand from the hypertrophied myocardium, and RV failure ensues. At the cellular level, there is evidence of cardiomyocyte proliferation, increased myocardial connective tissue, increased collagen synthesis, and development of fibrosis, ischemia, neurohumoral activation (sympathetic nervous and renin-angiotensin-aldosterone systems) and metabolic changes.

Analogies to Left Heart Failure

In pulmonary arterial hypertension (PAH), pathological remodeling of the pulmonary vasculature leads to increased pulmonary resistance and pressure, with subsequent development of right heart failure. However, it has been noted that mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) do not relate well to survival in PAH; rather, indices of right heart function better predict mortality[7–9]. The maladaptation of the heart in response to increased pressures is therefore the key contributor to mortality. Similarly, regardless of the cause of left heart failure, it has been recognized that the cardiac remodeling that ensues ultimately leads to disease progression[10]. As a result, treatment in all forms of left heart failure are aimed at preventing or reversing this pathologic

remodeling[11, 12]. Although the right and left ventricles differ embryologically, structurally, and physiologically, it has been hypothesized that many of the same pathophysiological events that occur in left heart failure are the same in right heart failure, with important implications for preservation of the RV in right heart failure[13].

Targeting the Right Ventricle

Neurohormonal Activation and Modulation

Activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS) in heart failure initially occurs in order to compensate for a reduced cardiac output. However, chronic activation of these systems has been recognized as ultimately promoting progression towards left heart failure via its effects on pathological ventricular remodeling[12, 14]. Hence, combination therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiogiotensin receptor blocker (ARB) and a β-blocker (typically carvedilol or metropolol succinate) are the mainstay of left heart failure treatment.

Evidence points to the upregulation of these systems in right heart failure, as well[15]. For example, various measures of increased sympathetic activity have been found to be abnormal in PAH patients, such as elevated plasma norepinephrine[16, 17], reduced cardiac uptake of meta-iodobenzylguanidine [18], increased post-ganglionic muscle sympathetic nerve activity[19], downregulation of the β1-adrenergic receptors in the RV[20], and reduced heart rate variability[21]. Similarly, there is evidence that the RAAS is elevated in patients with cor pulmonale and in animal models of PAH[22, 23]. However, despite the data that these systems are upregulated in right heart failure, thus far very little study has been done to evaluate the therapeutic effects of modulating these neurohormonal pathways in right heart failure.

While β-blockade is approved therapy in LV failure and has shown to improve morbidity and mortality, its use in RV failure is still not established. In fact, β-blockers are considered relatively contraindicated in PAH, due to concerns for the possible negative effect on these patients' hemodynamics and exercise capacity. This is based on a small study of 10 patients with portopulmonary hypertension, in whom withdrawal of propranolol was associated with improved exercise tolerance[24]. Another case report describes a patient with portopulmonary hypertension treated with β-blocker for supraventricular tachycardia that led to acute cardiovascular decompensation[25]. However, some emerging data suggest these drugs may be safe to use in RV failure and potentially efficacious in preventing dysfunctional right heart remodeling. For example, β-blockers have been shown to improve RV function and prevent myocardial remodeling in animal models of pulmonary hypertension[26, 27] as well as to reverse the characteristic "molecular signature" of RV failure[28].

In humans, a small single-arm study of beta-blockers in patients status-post correction of transposition of the great arteries showed improvement in symptoms, quality of life, and RV ejection fraction[29]. More recently, a prospective cohort study of 94 PAH patients found no increased adverse clinical or hemodynamic consequences in the 28% of those patients who were prescribed β-blockers for other cardiac comorbidities[30].

As mentioned previously, the renin-angiotensin-aldosterone system (RAAS) is also upregulated in heart failure as part of the compensatory responses that also promote disease progression. In heart failure, inhibition of RAAS by angiotensin converting enzyme (ACE) inhibitors can decrease pathological ventricular remodeling and mortality[31]. ACE inhibitors and ARBs have been shown to improve cardiac function, survival, and RV remodeling in preclinical models of right heart failure[32–37]. For example, Okada et al.

showed that the ACE inhibitor captopril decreases the development of RVH in the monocrotaline rat model and inhibits the expression of matrix metalloproteinase (MMP)-2 and MMP-9[37]. MMPs have been shown to be critical in the development of cardiac hypertrophy and heart failure via extracellular remodeling and are upregulated in monocrotaline-induced RV hypertrophy[38]. In another study, the same authors used temilsartan, an angiotensin receptor blocker, in monocrotaline-induced RVH rat model and again showed attenuation of RVH through improvement of RV hypertrophy, fibrosis, dysfunction and inhibition of MMPs[36]. Despite these recent advances, the potential benefit of beta-blockade and/or RAAS modulators in PAH and other forms of right heart failure still require additional investigation.

Cellular Metabolic Changes in RV Hypertrophy and Failure and Potential Modulators

Another potential RV target for therapy is the metabolic and mitochondrial remodeling seen in RVH. It has been long recognized that there is a shift from glucose oxidation to glycolysis in RVH. The glycolytic phenotype is associated with less ATP production; however it confers resistance to apoptosis, in part because the “inactive” hyperpolarized mitochondria cannot induce apoptosis. This metabolic shift can be detected by ^{18}F-fluoro-deoxy-glucose positron emission tomography (FDG-PET). Studies have demonstrated increased glycolysis in RVH in both humans and animal models using FDG-PET scans. For example, FDG accumulates in RV myocardium in PAH[39–42].

Dichloroacetate, an inhibitor of the mitochondrial pyruvate dehydrogenase kinase (PDK), has been used to improve glucose oxidation in RVH. In human and rat RVH, dichloroacetate reversed hyperpolarization of the mitochondrial membrane potential and increased RV inotropy[43]. In two models of experimental RVH, inhibiting PDK with dichloroacetate improved RV function and electrical remodeling[44]. Finally, dichloroacetate was shown to normalize action potential duration and QT interval changes that occur in RVH via partial resoration of Kv channel expression [44].

A Role for PAH-specific Therapies

Many therapies used for the treatment of PH are pulmonary vasodilators with no shown effect on RV except for PDE-5 inhibitors. Nagendran et al. showed increased PDE-5 expression in the myocardium of patients with RVH as well as in rat models of RVH. PDE-5 inhibition led to improved RV contractility and decreased RV afterload in RVH[45]. Another approved therapy for pulmonary hypertension is prostacyclin, which can act as a ligand for the intranuclear receptors PPARβ/δ, modulators of gene expression. Previous studies looking at PPARγ agonists showed protective effects in chronic hypoxia and monocrotaline models of PH in rats with reduction in pulmonary vascular remodeling. Harrington et al. evaluated PPARβ/δ agonist in a rat model of hypoxia-induced PH and showed a significant reduction in the associated RVH and RVSP but no effect on vascular remodeling in this model[46].

Given the complex pathogenesis of PAH and the multitude of cell types and signaling cascades associated with pulmonary vascular and RV remodeling, newer therapies being evaluated are targeting distal signaling mediators, such as histone deacetylases (HDAC). HDACs control cell proliferation, inflammation and fibrosis, and HDAC inhibitors are approved for cancer treatment. In LVH, HDAC inhibitors were shown to be efficacious, but in one study using a model of pulmonary artery banding, HDAC inhibition was associated with RV dysfunction and worsened remodeling[47]. In a more recent study, a more selective class 1 HDAC inhibitor was used in hypoxic rat model of PH and showed modest reduction in RV hypertrophy but more importantly it suppressed the expression of pathological genes, inhibited caspase activity and the expression of proinflammatory protein expression[48].

Similarly, imatinib, a tyrosine kinase inhibitor being evaluated for the treatment of PAH, has been shown to have an effect on RV. In two animal models of PAH, treatment with imatinib reversed RVH supporting an antiremodeling, antiproliferative effect[49].

Stem cell therapy has also been evaluated as a new treatment modality for patients with PAH. Several groups have looked at stem cell therapy in experimental models of PAH using different cell populations but showed lower PA pressures, less RVH and improved survival. Umar et al. used bone marrow derived mesenchymal stem cells from rats with MCT-induced PAH to treat recipient rats with MCT-induced PAH. They showed that mesenchymal stem cell treatment reduced lung pathology, decreased RVH and improved RV function[50].

Lastly, another experimental therapeutic option that has been explored is right ventricular pacing. In a well-conducted study, Handoko et al. studied the effects of RV pacing and showed improved RV systolic function and diminished adverse diastolic interaction with LV[51].

Conclusion

The right ventricle plays a central role in PAH and congestive heart failure. Nonetheless, the management of RV dysfunction and failure remains a challenge. Recent work has advanced our understanding of the mechanisms underlying the transition from compensated RVH to maladaptive remodeling. Targeting these pathways should guide the development of RV-specific therapies.

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Table 1

Preclinical Studies of Right Ventricle Targeted Therapies

Therapy	Major findings	Reference
MCT-induced PH rat model		
β-blocker	Reversed RV remodeling and improved RV function. Attenuated the progression of PAH and prevented RVH. Delayed progression to RVF and preserved RV function.	Bogaard et al. Ishikawa et al. deMann et al.
ACE Inhibitor	Attenuated the development of RVH.	Okada et al.
Angiotensin receptor blockade	Attenuated the development of RVH.	Okada et al.
Phosphodiesterase-5 inhibitor	Improved RV contractility and decreased RV afterload	Nagendran et al.
Tyrosine kinase inhibitor	Reversed RVH	Schermuly et al.
Stem cell therapy	Decreased RVH and improved RV function	Umar et al.
Right ventricular pacing	Improved RV systolic function	Handoko et al.
Dichloroacetate	Increased RV inotropy Improved RV function and electrical remodeling	Nagendran et al. Piao et al.
PA banding PH rat model		
Dichloroacetate	Improved RV function and electrical remodeling	Piao et al.
Hypoxia-induced PH rat model		
β-blocker	Reversed RV remodeling and improved RV function.	Bogaard et al.
PPARβ/δ agonist	Reduced RVH and RVSP	Harrington et al.
Selective class I histone deacetylase inhibitor	Reduced RVH	Cavasin et al.

Table 2

Clinical Studies of Right Ventricle Targeted Therapies

Therapy	Design	Population	Major findings	Reference
β-blocker (bisoprolol, carvedilol)	Single-arm, open-label	Patients status-post correction of transposition of the great arteries	Improved symptoms, quality of life, and RV ejection fraction.	Bouallal et al.
β-blocker (metoprolol, atenolol, bisoprolol, propranolol, acebutolol, nodolol)	Prospective cohort study	PAH patients	Did not increase adverse or hemodynamic consequences.	So et al.
β-blocker (metoprolol)	Case report	Portopulmonary hypertension	Caused hemodynamic compromise	Peacock et al.
β-blocker (propranolol, atenolol)	Prospective cohort study	Portopulmonary hypertension	Withdrawal of β-blocker caused improved exercise capacity and hemodynamics	Provencher et al.