Molecular Mechanisms of Right Ventricular Failure

Sushma Reddy, MD; Daniel Bernstein, MD

Abstract—An abundance of data has provided insight into the mechanisms underlying the development of left ventricular (LV) hypertrophy and its progression to LV failure. In contrast, there is minimal data on the adaptation of the right ventricle (RV) to pressure and volume overload and the transition to RV failure. This is a critical clinical question, because the RV is uniquely at risk in many patients with repaired or palliated congenital heart disease and in those with pulmonary hypertension. Standard heart failure therapies have failed to improve function or survival in these patients, suggesting a divergence in the molecular mechanisms of RV versus LV failure. Although, on the cellular level, the remodeling responses of the RV and LV to pressure overload are largely similar, there are several key differences: the stressed RV is more susceptible to oxidative stress, has a reduced angiogenic response, and is more likely to activate cell death pathways than the stressed LV. Together, these differences could explain the more rapid progression of the RV to failure versus the LV. This review will highlight known molecular differences between the RV and LV responses to hemodynamic stress, the unique stressors on the RV associated with congenital heart disease, and the need to better understand these molecular mechanisms if we are to develop RV-specific heart failure therapeutics. (Circulation. 2015;132:1734–1742. DOI: 10.1161/CIRCULATIONAHA.114.012975).

Key Words: angiogenesis • heart defects, congenital • heart failure • hypertrophy • oxidative stress
direct effects on the RV, independent of those attributable to pressure overload. The structural and functional similarities and differences in the RV and LV responses to abnormal loading conditions have been discussed in the review series on “Challenges and Opportunities in Pediatric Heart Failure.”

This review is a part of the same series and will highlight the molecular changes in the RV response to stress, our current knowledge of how the RV adapts to the unique hemodynamic stressors experienced by patients with CHD, and the need to better understand the molecular mechanisms of RV failure, providing new targets for the development of RV-specific heart failure therapeutics. Finally, the progression of the RV from a compensated to a decompensated state is often difficult to follow clinically, given the limitations of noninvasive imaging in assessing RV contractile function. Planning for surgical interventions, eg, pulmonary valve replacement, may be enhanced if serum biomarkers marking the earliest stages of RV failure could be developed to use in conjunction with imaging data.

Is the Response to Afterload Stress of the RV Different From That of the LV?

The fundamental differences in the mechanisms of RV versus LV failure are best demonstrated by the divergence in the response of the 2 ventricles to heart failure therapies, particularly when treating systemic RV failure in CHD (patients with single-ventricle physiology or with a systemic RV as in l-TGA or d-TGA after atrial switch). Multiple clinical trials have shown that standard heart failure drugs (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers), developed and tested in patients with LV failure, do not improve function or survival in patients with systemic RV failure attributable to CHD; and, in at least 1 trial, β-blockers seemed to worsen outcomes in patients with a systemic RV.

Long-term survival studies also show that patients who have single-ventricle physiology with a systemic RV progress to heart failure sooner and more often than those with a systemic LV.15 Patients with l-TGA, where the RV functions as the systemic ventricle, have an increased risk of RV failure as they age, even in the absence of atrioventricular valve regurgitation or other lesions. Similarly, the systemic RV is at risk in patients who have undergone an atrial switch operation for d-TGA. These systemic RVs develop hypertrophy, usually at a very early age, and therefore increased wall stress alone cannot be the only factor predisposing these ventricles to failure.

In the past, differences in global structure and loading conditions were thought to represent the main differences between the RV and LV.16 These structural and physiological differences have been reviewed by Friedberg et al19 earlier in this series. We now recognize that these differences begin early in development, before afterload differences become operative (remember that the fetal RV and LV are both coupled to the systemic circulation). This divergence begins with the primary and secondary heart fields, leading to the differentiation of LV or RV cardiomyocytes during early development, and continues with chamber-specific differences in cell signaling and Ca2+ handling, all suggesting fundamental differences between the 2 ventricles at the cellular level as well.17

We and others have shown differences at the cellular and molecular levels in the RV versus LV responses to pressure overload stress. Although the 2 ventricles exhibit similar alterations in genes regulating extracellular matrix and cytoskeletal remodeling, there are important differences in genes regulating energy production, mitochondrial function, reactive oxygen species (ROS) production and antioxidant protection, and angiogenesis (Table).18,19 These results confirm differences at the cellular and molecular level in the mechanisms leading to heart failure between the 2 ventricles. We will discuss each of these differences below.

RV Molecular Remodeling: Adaptive and Maladaptive Responses

Metabolic Adaptations to Pressure Overload

The RV and LV differ in their workload, and hence in their energy needs. Based on ventricular afterload alone, the LV workload is 5 times greater than the RV because of the higher systemic vascular resistance in comparison with the low-resistance pulmonary vascular bed. The resistive and capacitive components of RV afterload have been detailed in earlier reviews.10,20 We will therefore focus on the metabolic consequences of this afterload. Because of this decreased workload on the resting RV, both oxygen consumption and metabolic stress (ATP generation rate/maximum ATP generation rate) are lower than in the LV.21,22 Despite this difference, in the nonstressed state, the RV and LV are largely similar in their energetic profiles, including glycolytic, tricarboxylic acid cycle, oxidative phosphorylation enzyme activities, cellular aerobic capacity, and volume fraction of mitochondria, with the exception being a slight decrease in fatty acid–binding protein (FABP) in the RV.

Afterload stress induces alterations in the metabolic profile of both ventricles. Both the RV and LV myocardium use free fatty acids for biosynthesis and energy production in the normal fasting state. With the onset of hypertrophy, however, the myocardium shifts to a greater dependence on glucose for its energy source via increased glucose uptake and glycolysis, because there is less oxygen consumed per ATP generated in comparison with fatty acid metabolism. Although this shift is beneficial during acute stress, chronic dependence on glycolysis for energy production is inadequate to meet the demands of the myocardium and to maintain normal function, leading to an energy-starved state and contributing to heart failure.

In RV failure following pulmonary artery banding (PAB), this shift in glycolysis is mediated by changes in aldolase, hexokinase, pyruvate kinase, and glucose-6-phosphate dehydrogenase, a switch in lactate dehydrogenase isoforms toward anaerobic glycolysis and a 50% decrease in energy reserve.24 Decreased glucose oxidation is also related to the activation of pyruvate dehydrogenase kinases, which inhibit pyruvate dehydrogenase, preventing pyruvate from entering the Krebs cycle and increasing reliance on glycolysis for ATP generation. Inhibition of pyruvate dehydrogenase kinases by dichloroacetate has been shown to improve glucose oxidation and RV function in rat models of PHTN.18 Partial inhibition
of β-oxidation by trimetazidine has been shown to improve both LV and RV function in patients with diabetic cardiomyopathy. No data exist on their role in models of CHD. Hypoxia-inducible factor-1α (Hif-1α) and p38 mitogen-activated protein kinase are also activated when the RV begins to fail, and both have been shown to increase glycolysis. Hif-1α activation is also associated with complex II–mediated ROS production. In a murine model of acute, severe PAB-induced RV failure, we showed a downregulation of mitochondrial DNA with failure in CHD. However, the switch to glycolysis appears to occur earlier in the pressure-loaded RV versus the pressure-loaded LV, resulting in an earlier decrease in net ATP production in the RV. If energetic pathways are more at risk in the chronic pressure-loaded RV, then strategies that maintain favorable ATP production and oxygen consumption may be beneficial. Several drugs that increase glucose use (ranolazine, trimetazidine, perhexiline) have been tested in animal models of PHTN and in human clinical trials of LV failure and PHTN-induced RV failure, with variable success. There are few data on the metabolic derangements in CHD and no data on the utility of drugs to modify these alterations. Cardiac metabolic imaging, eg, magnetic resonance spectroscopy, has the potential to shed more light on alterations in RV metabolism in patients with CHD. However, the thin free wall of the normal RV makes obtaining control data for comparison a challenge. Important differences on calcium handling, heart rate, and metabolism exist between animal models and patients, thereby limiting direct translation. However, the use of animal models is the first step toward understanding the mechanism of disease. Patients with right heart failure attributable to PHTN show a metabolic shift away from fatty acid metabolism to glycolysis, and abnormalities in mitochondrial complexes 1, III, and IV have been described in children with CHD, notably tetralogy of Fallot. This is similar to what has been demonstrated in animal models of PAB and PHTN, making it feasible to use animal models to study the mechanism of disease.

### Table. Summary of Key Findings in the Right Ventricle During Rest, Hypertrophy, and Failure

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Effect of RV Hypertrophy and Failure</th>
<th>Significance in the RV</th>
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<tr>
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<td></td>
<td>↑ Glycolysis</td>
<td>↑ Mitochondrial ROS production</td>
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<tr>
<td></td>
<td>↓ Mitochondrial complex 1, III, IV.</td>
<td>↑ NADPH oxidase mediated ROS production</td>
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<tr>
<td></td>
<td>↓ Resting mitochondrial membrane potential; hyperpolarized with hypertrophy.</td>
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<tr>
<td></td>
<td>↓ Mitochondrial DNA with failure in CHD.</td>
<td>NADPH oxidase mediated ROS production</td>
<td></td>
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<tr>
<td>Oxidative stress</td>
<td>↑ Hif-1α activation and complex II–mediated ROS production.</td>
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<td></td>
<td>Antioxidant enzymes (SOD, GPX) are not activated with hypertrophy</td>
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<td>↑ Mitochondrial ROS production</td>
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<td>Positive α1-signaling (nonstress) attributable to ↑ myofilament Ca2+ sensitivity.</td>
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<td>↑ Coupling of [2] receptors to Gs</td>
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<td>↓[2]–oxidation by trimetazidine has been shown to improve</td>
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<td>↓ Angiogenic response</td>
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<tr>
<td>Response to hypoxia</td>
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<td>Positive α1-signaling (nonstress) switches to positive (failure).</td>
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<tr>
<td></td>
<td>↑ Coupling of β2 receptors to Gs</td>
<td>↑[2]-receptor mediated inotropy and lusitropyα</td>
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<td></td>
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<td>Negative α1-signaling (nonstress) switches to positive (failure).</td>
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<td>↓ Angiogenesis</td>
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**CHD** indicates congenital heart disease; FABP, fatty acid–binding protein; GPX, glutathione peroxidase; GRK, G protein–coupled receptor kinase; miR, micro-RNA; MLCK, myosin light chain; RAAS, renin-angiotensin-aldosterone system; ROS, reactive oxygen species; SOD, superoxide dismutase; and VEGF, vascular endothelial growth factor.
Metabolic Response to Chronic Volume Overload

If our knowledge of the RV response to pressure overload is limited, then our knowledge of the RV response to volume overload, a common late sequela after RV outflow tract reconstruction, single RVs with an aortopulmonary shunt, or l-TGA with atrioventricular regurgitation, is almost nonexistent. To address this shortcoming, we developed a murine model of chronic RV volume overload, induced by suturing 2 of the pulmonary valve leaflets to the pulmonary arterial wall.33 During the early stages of RV volume overload, there is diastolic dysfunction and preserved systolic function, at which point there is downregulation of several metabolic pathway regulators, including phosphofructokinase, a rate-limiting enzyme in glycolysis, and aconitase, an upstream tricarboxylic acid cycle enzyme, both important for ATP production. There are also decreases in genes encoding transport of nutrients across the cell membrane such as ATP-binding transporters. During the later stages of RV volume overload, there is worsening of diastolic dysfunction and the onset of fibrosis, but, similar to the clinical situation, systolic function at this stage is largely preserved. There is a shift away from β-oxidation with downregulation of fatty acid–binding protein and upregulation of AMP kinases, and increased glycogenolysis with upregulation of glycogen synthase kinase-3β and glycogen phosphorylase. These adaptations are similar to those described during LV volume overload; however, additional research will be required to determine whether more subtle differences exist.

ROS Production and Antioxidant Defenses

At rest, the mitochondrial protein profiles of the RV and LV are quite similar, diverging only when subjected to afterload stress. A proteomic analysis of the normal rabbit and porcine RV and LV free walls shows equivalent cellular aerobic capacity, volume of mitochondria, mitochondrial enzyme content (cytochrome c oxidase, complexes 1, 3, 4, and 5, aconitase, and manganese-dependent superoxide dismutase) and mitochondrial enzyme activities.23

Mitochondrial membrane potential, a surrogate of overall mitochondrial function, is lower in the resting RV than in the LV but increases with RVH. This hyperpolarization is related to an activation of the nuclear factor of activated T cells pathway and is reversed by dichloroacetate, an inhibitor of pyruvate dehydrogenase kinases (discussed above). The difference in mitochondrial remodeling may represent another difference in the stress response between the RV and the LV, and another potential target for RV-specific therapy.33

Under conditions of afterload stress, both ventricles increase ROS production; however, in the RV antioxidant defenses fail early, whereas in the LV they remain intact until a more advanced stage of failure.34,35 In fact, during pressure overload–induced left ventricular hypertrophy, antioxidant enzymes are actually activated during the initial compensated stage, decreasing during the onset of failure, and resulting in increased ROS-related damage and apoptosis. In contrast, in the PHTN-stressed RV, the antioxidant enzymes superoxide dismutase and glutathione peroxidase are not activated at all in the compensated stage, predisposing the RV to ROS-induced damage at an earlier stage than in the LV.36 In our murine model of PAB-induced RV failure, we found even earlier downregulation of antioxidant enzymes and increased ROS production (unpublished data). Of note, the antioxidant EUK-134 (a superoxide dismutase and catalase mimetic) reduces oxidative stress and ROS production in the failing RV attributable to PHTN and improved RV systolic function.37

There are also differences between the 2 ventricles in the primary source of ROS production. In the RV, NADPH oxidase and mitochondrial complex II activity both increase, whereas, in the LV, NADPH oxidase is the primary source of ROS generation, suggesting greater mitochondrial ROS generation in RV failure. As mentioned earlier, Hif-1α activation is associated with complex II–mediated ROS production in RVH.38 Another key regulator that is decreased during RV failure is PGC1α, leading to impaired fatty acid oxidation, decreased mitochondrial mass and number, and reduced oxidative capacity. This represents another mechanism leading to increased ROS production, causing mitochondrial DNA damage and further altering mitochondrial biogenesis.39,40

Confirming these experimental findings in patients, Karamanlidis et al41 demonstrated a progressive decline in mitochondrial DNA with the progression from RVH to RV failure in children with CHD which included children with tetralogy of Fallot, pulmonary stenosis, double-outlet RV, double-chambered RV, and single RV. Increased transcription of mitochondrial DNA–encoded genes responsible for mitochondrial biogenesis falls before the onset of heart failure.

Blood Flow and Angiogenesis

The RV has a lower resting oxygen consumption and therefore lower resting coronary blood flow than the LV. In the normal RV, the majority of coronary flow occurs in systole, in contrast to the normal LV where coronary flow is mostly in diastole. During RV afterload stress, some have described increased right coronary artery flow and increased oxygen extraction to support the increased oxygen demand of the hypertrophied RV, whereas others have reported increased right coronary flow but impaired oxygen extraction.21,42

When stressed, the RV is more susceptible to ischemia. Ohuchi et al,42 using 3-dimensional micro-computed tomography in a porcine model, demonstrated a reduced microvascular bed in the RV in comparison with the LV. With development, there is an increase in both arteriolar length and the number of vessel generations in both the RV and LV. However, the number of generations plateaus earlier in the RV than in the LV, and the perfused volume/cross-sectional area is significantly lower in the mature RV. These differences may represent a functional reserve needed by the LV to account for the higher intramural pressure and the greater variability in its workload. Thus, LV coronary flow may increase by up to 5-fold to support increased demand in both the normal and pressure-overloaded LV.43 Unique to the RV, with its systolic coronary perfusion, progressive increases in RV systolic pressure relative to aortic systolic pressure reduce coronary perfusion, rendering the pressure-overloaded RV more susceptible to ischemia than the pressure-overloaded LV.

This RV susceptibility to ischemia is compounded by an impaired angiogenic response to pressure overload in comparison with the LV. In the pressure-overloaded LV, the effects of compensatory angiogenesis are still controversial. Sano et
al showed that, in mice undergoing aortic banding, activation of Hif-1α and vascular endothelial growth factor (VEGF) induces angiogenesis, increasing the capillary/myocyte ratio during the phase of adaptive hypertrophy. During the transition to LV failure, p53 increases, which suppresses Hif-1α and leads to decreased capillarity. In contrast, Choi et al demonstrated the activation of Hif-1α during adaptive pressure overload in the rabbit LV but without associated VEGF activation, and a decrease in capillarity secondary to the release of antiangiogenic factors from the breakdown of the extracellular matrix. In a model of compensated left ventricular hypertrophy that does not progress to heart failure, we found no evidence that angiogenic mediators play a role: HIF-1α, VEGF, and capillarity were all unchanged.

In the pressure-overloaded RV, the angiogenic response differs based on the stimulus. In monocrotaline-induced PHTN, there is an increase in capillarity, whereas in PAB models there is activation of Hif-1α, but surprisingly a decrease in VEGF and unchanged capillarity. Thus, reduced coronary perfusion, exacerbated by a failure of angiogenic upregulation in the setting of hypertrophy, may exacerbate RV ischemia, possibly one of the triggers for the metabolic shift from mitochondrial oxidative phosphorylation to glycolysis described possibly one of the triggers for the metabolic shift from mitochondrial oxidative phosphorylation to glycolysis described earlier. Reduced ATP generation results in the failure to meet the increased oxygen demands of the hypertrophied RV and leads to RV failure. Other adaptations might be beneficial for the stressed RV, eg, endogenous release of nitric oxide mediates right coronary artery vasodilation, thereby improving oxygen demand-supply balance, not the case in the LV.

Thus, whether differences in RV versus LV oxygen delivery and microvascular remodeling are responsible for the differences in stress response between the 2 ventricles is still an area open to further investigation.

Response to Hypoxia
Myocardial hypertrophy uncouples VEGF signaling and angiogenesis and may be another contributor to the progression to RV failure. In SUGEN-hypoxia–induced PHTN, hypoxia activates Hif1α/VEGF signaling in the RV, but, as in pressure overload alone, without increasing capillary density. This is particularly relevant in systemic RVs exposed to hypoxia such as in infants with hypoplastic left heart syndrome after a Norwood/Sano or Glenn palliation, where the RV is hypertrophied and has increased metabolic demand because of its function as the systemic ventricle, but fails to increase capillary density to enhance delivery of oxygen and nutrients. Early hypoxia also triggers glycolysis, but, after several weeks myocardial metabolism, reverts back to fatty acid oxidation. When myocardial metabolism reverts again to glycolysis is unclear, but the timing may correlate with the development of RV failure.

Neurohormonal Activation: Adrenergic Receptors
Although β-adrenergic receptor signal regulation appears to be similar in the failing RV versus the LV, the clinical response of the 2 ventricles to β-adrenergic blockers is quite different. In the normal RV, β-adrenergic receptor stimulation induces similar positive inotropic responses as in the normal LV. In RV failure, secondary to PHTN or PAB, there is downregulation of β1-, α1-, and DA1 receptors, decreased cAMP levels, and increased G protein–coupled receptor kinase-2 activity, leading to an impaired inotropic response. This downregulation of adrenergic signaling is greater in PHTN-induced than in PAB-induced RVH. Therefore, it would seem to make sense that β-blockade should have a therapeutic benefit in the failing RV. However, as discussed above, there is no evidence for the utility of β-blockers in children with systemic RVs and even a suggestion that this class of drugs can worsen heart failure symptoms. Similarly, in adults with RV failure after repaired tetralogy of Fallot, β-blockade showed no improvement in peak VO2, RV ejection fraction, ventricular volume, or New York Heart Association class. One study stands in contrast, a retrospective study of adults with a systemic RV and mild (New York Heart Association class I and II) symptoms, who did show an improvement, but only if they were taking a β-blocker for at least 4 months. The concomitant presence of pressure overload in the failing RV may result in upregulation rather than downregulation of RV β-receptors. In these patients, there was also enhanced coupling of β2 receptors to Gs, resulting in increased β2-receptor–mediated inotropy and lusitropy.

Another difference between the RV and LV is in α1-adrenergic signaling. In nonstress situations, the stimulation of α1-receptors results in a negative inotropic response in the RV and a positive inotropic response in the LV. This differential response is not mediated by differences in protein kinase C activation, but instead by a greater myofilament Ca2+ sensitivity through phosphorylation of myosin light chain in the LV versus the RV. However, in the failing RV, myosin light chain increases, resulting in a greater myofilament Ca2+ sensitivity, and α1-signaling then switches from being a negative to being a positive inotrope. These studies were performed in failing RVs attributable to coronary artery ligation; therefore, its applicability in RV failure attributable to CHD remains to be determined.

Neurohormonal Activation: Renin-Angiotensin-Aldosterone System
Activation of the renin-angiotensin-aldosterone system (RAAS) occurs in the setting of low LV cardiac output and low systemic vascular resistance, causes vasoconstriction and increased tubular sodium reabsorption peripherally, and also has direct effects on cardiomyocyte fibrosis. The RAAS has not been fully evaluated in RV failure other than by a few studies in chronic obstructive pulmonary disease and systemic sclerosis causing PHTN. More recent data demonstrate RV RAAS activation in patients with PHTN with a decrease in hypertrophy and restoration of RV-arterial coupling with losartan treatment. Treatment with angiotensin-converting enzyme inhibition, however, has conflicting results, which are thought to be related to breakthrough aldosterone signaling from incomplete inhibition. Whether the RAAS is stimulated with RV failure in the setting of CHD remains to be determined; this is particularly important because angiotensin-converting enzyme inhibitors (enalapril, ramipril) and
angiotensin II receptor antagonists (losartan) have failed to improve right heart failure in CHD patients with a systemic RV.\textsuperscript{14,63–65} Although clinical trials are currently evaluating the efficacy of losartan in adults with tetralogy of Fallot and RV failure, a better understanding of the basic mechanisms of RAAS activation in the stressed RV needs to be concurrently undertaken.

**Micro-RNAs**

Micro-RNAs (miRs) are small, noncoding RNAs of 18 to 25 nucleotides that regulate gene expression by degradation or translational suppression of mRNA. As master regulators of entire gene networks, miRs have received considerable attention in cardiovascular development and in LV hypertrophy and failure and are being developed as therapeutic targets and as biomarkers to monitor disease progression.\textsuperscript{66–68}

There are interesting differences in miR expression between the RV and LV. The prevalence of specific miRs in the resting RV is quantitatively different from that in the LV, and this difference is maintained during afterload stress (Figure). We profiled miR expression at various stages of adaptive RVH progressing to RV failure. Although most of the upregulated miRs are similar to those in LV afterload stress, we found 4 RV-specific miRs: miRs 34a, 28, 93, and 148a, none of which are increased in LV hypertrophy and failure induced by transverse aortic constriction.\textsuperscript{69–72} These miRs cause cell cycle arrest, oxidant damage, and impairment of DNA repair, and they inhibit proangiogenic factors, as well.\textsuperscript{73} Interestingly, miR-34a is upregulated in the LV, but only during ischemia. These data suggest that, in the pressure-loaded RV, which, as noted earlier, is more susceptible to ischemia, miR-34a signaling may be more akin to that in LV ischemia than in left ventricular hypertrophy.\textsuperscript{41} All 4 RV-specific miRs are upregulated only in noncardiomyocytes, but appear to have their greatest effect on cardiomyocytes, possibly through paracrine effects. These RV-specific miRs may enhance the progression to RV failure by increasing oxidative stress, reducing oxidative defenses, decreasing angiogenesis, and activating cell death pathways, the very pathways that differ most between the RV and LV. Potus et al\textsuperscript{74} suggest a systemic vascular defect in PHTN in the endothelial cells of the pulmonary artery and the RV through the miR-126/VEGF pathway. This pathway was upregulated during compensated RVH but transitioned to being downregulated with RV failure. A downregulation in miR-208 followed by an upregulation of its target Mef2 has also been described in RV failure secondary to PHTN.\textsuperscript{75,76}

**Models of RV Failure Simulating Residual Lesions After RV Outflow Tract Reconstruction**

We have created murine models of RV pressure overload, volume overload, and combined pressure and volume overload to simulate some of the common residual lesions seen after RV outflow tract reconstruction, thereby enabling the assessment of genomewide changes in the RV during the transition from RVH to RV failure. These models show a progression from a compensated, adaptive stage with predominant diastolic

![Figure](http://circ.ahajournals.org/)

**Figure.** The 10 most abundantly expressed miRs in the RV of sham and PS animals were compared with the 10 most abundant miRs in the LV of sham and SRF-induced hypertrophy. Data are expressed as median signal intensity. LV data were obtained from GEO data sets. Micro-RNA (miR) distribution is similar in both the RV and LV with miR-1, 133, and let-7 family being the most abundant. LV indicates left ventricle; LVH, left ventricular hypertrophy; RV, right ventricle; and RVH, right ventricular hypertrophy. Reprinted from Reddy et al.\textsuperscript{75}
dysfunction to decompensated systolic dysfunction with clinical heart failure.

Pressure overload was characterized by the upregulation of genes regulating phosphate and other inorganic ion transport, cell adhesion, and cell death pathways. Although most of these transcriptional changes were similar between the RV and LV, there were several genes that were upregulated in the pressure-overloaded RV that were not altered in the pressure-overloaded LV, including genes involved in Wnt signaling (Dickkopf 3, Sfrp2, and Wif1), annexin A7, clusterin/apolipoprotein J, neuroblastoma suppression of tumorigenicity 1 (Nbl1), formin-binding protein (Fnbp4), and LOX. Metabolic pathways dominated the downregulated gene pathways. Whether these differences in the RV versus LV are related to their different geometric structures, to markedly different afterloads, or to basic differences in cardiomyocyte biology will be the subject of future research.

The gene expression changes in the volume-loaded RV versus LV are largely similar. We next compared the gene expression changes induced by RV volume overload with those induced by RV pressure overload. There were many similarities, representing pathways involved in regulating extracellular matrix remodeling, the actin cytoskeleton, and metabolism, although most transcripts were not as highly expressed in RV volume overload as in pressure overload.

The development of animal models of chronic RV failure is critical, because they may better represent the clinical course of patients with CHD, as opposed to models where failure occurs within a few weeks. Such models will also be ideal for therapeutic trials because they are in a stable, compensated phase of diastolic dysfunction but have changes that render the myocardium vulnerable to injury, predisposing to systolic dysfunction. Improving energy efficiency and arresting cell death and fibrosis are areas to target for new therapeutics. We need to work closely with our surgical colleagues to ensure the collection of all resected human tissue from children and adults with CHD to further dissect important pathways identified in the animal models.

RV diastolic dysfunction is well described in children with CHD with residual pressure and volume overload lesions. What causes diastolic dysfunction is poorly understood. Diastolic dysfunction in the RV secondary to PHTN in humans is associated with cardiomyocyte hypertrophy and fibrosis from collagen deposition. The increased sarcomeric stiffness was attributed to decreased phosphorylation of titin, a major sarcomeric protein. Animal models with chronic RV diastolic function may aid in better understanding the mechanism of diastolic dysfunction.

Conclusions

Although there are considerable data on the mechanisms of LV dysfunction and failure, the pathways mediating the transition from a compensated stage to failure are still not well defined. We are only now beginning to understand the mechanisms of RV dysfunction and remodeling. Defining a molecular mechanism for the increased susceptibility of the RV in patients with CHD to progress from a compensated stage to failure would provide the basis for developing RV-specific heart failure therapies, a critical need given that standard LV failure therapies are ineffective in RV failure. Although serum biomarkers have not provided clear guidance for LV failure, identifying and developing new biomarkers of the progression from RV pressure/volume overload to failure should be considered, given the limitations of clinical assessment and imaging modalities (echocardiography, MRI) in determining the optimal timing for surgical intervention.

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Disclosures

None.

References


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