Ventricular failure manifests in many forms, its underlying physiology ranging from overt left ventricular (LV) systolic dysfunction to isolated right ventricular (RV) diastolic dysfunction, and the wide portfolio of resulting symptoms vary from chronic fluid retention to acute multiorgan dysfunction and death. In this review, we discuss the morphological, functional, and molecular similarities and differences in RV and LV responses to adverse loading and failure. We further discuss whether LV and RV function and failure can truly be discussed as separate entities and thereby examine interactions between the ventricles that on one hand contribute to ventricular dysfunction but on the other may be harnessed for therapeutic benefit.

Embryological and Physiological Differences Between the RV and LV

The RV and LV have different embryological origins.1 The LV originates from the primary heart field; the RV, from the secondary heart field. Consequently, several genes specifically control RV formation, including, among others, Hand2 and Tbx20.2 During gestation, the RV functions as the systemic ventricle (Figure 1A). During fetal life, in addition to supplying the modest amount of pulmonary blood flow, the RV pumps blood to the lower body and placenta and contributes more than half of the combined cardiac output.3 With the transition from fetal to postnatal physiology and with the reduction in pulmonary vascular resistance, the subpulmonary RV transforms its morphology and geometry, becoming a thin-walled chamber to adopt its postnatal physiological characteristics.4 Because it faces a low impedance pulmonary circulation, the normal postnatal RV maintains a cardiac output equal to that of the LV at approximately a fifth of the energy cost. The trapezoidal RV pressure-volume loop reflects this difference, with few if any isovolumic periods. Consequently, RV output starts early during pressure generation and is later maintained by a “hangout period”5 when antegrade flow continues into the pulmonary artery despite the onset of RV relaxation.5 In contrast, the rectangular LV pressure-volume loops reflect the LV square-wave pump function with distinct and well-developed isovolumic contraction and relaxation periods.6 Likewise, RV myocytes display faster twitch velocities than LV myocytes.7

The physiological differences are reflected in morphological differences between the ventricles (Table 1). The low-pressure RV is triangular in the sagittal plane and crescent-shaped in cross section as a result of the concave RV free wall and convex interventricular septum wrapping around the high-pressured, thick-walled, bullet-shaped LV. Consequently, although the normal RV has a lower ratio of volume to surface area and a thinner wall than the LV,8 the low cavity pressure determines a lower wall stress and lower oxygen demands.

Anatomic differences are also apparent in myocardial architecture. LV subepicardial and subendocardial fibers are oblique and helical with fiber angles ranging from 30° to 80° with a mean of ≈60°, whereas the midmyocardial myocytes are oriented predominantly in the short-axis plane of the equator with fiber angles of 20° to −20°.9 As a result, LV contraction is predominantly circumferential and radial with additional rotational and twisting motion. RV myocytes are predominantly longitudinal, creating a peristaltic contraction from the inlet to outlet and a bellows-like motion of the free wall toward the septum.10 That the ventricles differ in their anatomy and physiology is irrefutable, but as we discuss later, morphologically and functionally, they are inextricably linked not only in health but also as they react to disease.

Does the RV Differ From the LV in Its (Mal) Adaptation to Adverse Loading?

Although the RV is not immune to the direct effects of coronary disease with resulting global or regional ischemia, in clinical practice, RV physiology and failure are most frequently affected by increased preload or afterload. Adverse loading also affects LV function, but the RV is exquisitely dependent on, in particular, afterload. Even small changes in total pulmonary vascular resistance, as demonstrated by modest increases in mean airway pressure during positive pressure ventilation, can reduce RV contractile performance and lower cardiac output even when RV preload is maintained.11 In animal models, even modest increases in afterload lead to profound decreases in RV stroke volume.12 In contrast, much larger changes in LV afterload induced only modest

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changes in LV stroke volume. These experimental differences are reflected in clinical practice. Although patients with acute increases in systemic vascular resistance can compensate over a wide range, patients with acute pulmonary arterial hypertension (PAH), for example, in the setting of acute lung failure, frequently develop overt right heart failure and compromised cardiac output.

Although when acute even modest increases in RV afterload cause dramatic reductions in RV output in most clinical scenarios, including PAH and RV outflow obstruction, changes in afterload are chronic and occur progressively. Indeed, in the chronic setting, the relative increase in RV afterload is much greater in PAH than the increase in LV afterload in systemic hypertension. The question becomes, Can the RV adapt to increased afterload, and is this response adaptive or maladaptive? This question relates to another question: What is RV failure? If RV output is maintained over a wide range, patients with acute pulmonary arterial hypertension (PAH), for example, in the setting of acute lung failure, frequently develop overt right heart failure and compromised cardiac output.

Although we have emphasized the vulnerability of the RV to increased afterload, especially when acute, it is clear from clinical experience (eg, congenitally corrected transposition of the great arteries, Eisenmenger syndrome, systemic pulmonary shunts) that the RV can maintain function and adequate output in the face of systemic pressure over prolonged periods.

Eisenmenger syndrome is an interesting example of RV adaptation to continuous system-level resistance from fetal life and throughout postnatal life. In contrast to the normal RV, the Eisenmenger RV myocardium never thins. Consequently, RV and LV wall thicknesses are similar from fetal to adult life (Figure 1B). Patients with Eisenmenger syndrome have better RV function, higher cardiac index, and lower mortality than patients with other causes of PAH, despite a higher pulmonary vascular resistance. Therefore, it would seem that the RV has some capacity to retain fetal characteristics and to maintain adequate function in the face of systemic resistance over many years. Likewise, patients with a systemic RV after an atrial switch procedure for transposition of the great arteries or congenitally corrected transposition of the great arteries can live for decades. At the same time, it is also apparent that these patients are prone to RV failure and increased mortality, although arrhythmias and tricuspid regurgitation are important drivers of morbidity and mortality beyond RV myocardial failure per se (Figure 2).

### Differences Between the Left and Right Ventricles Under Normal Conditions

<table>
<thead>
<tr>
<th>Evolutionary development</th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryological origin</td>
<td>Primary heart field</td>
<td>Secondary heart field</td>
</tr>
<tr>
<td>Morphological characteristics</td>
<td>Bullet shape; prolate ellipsoid</td>
<td>Complex, crescentic</td>
</tr>
<tr>
<td>Myocardial characteristics</td>
<td>Thick smooth walls; fine trabeculations</td>
<td>Thin, heavily trabeculated walls</td>
</tr>
<tr>
<td>Myocardial architecture</td>
<td>Predominant radial myocyte orientation in the midlayers; subendocardial myocytes follow right-hand helix configuration; subepicardial myocytes form left-hand helix</td>
<td>Predominant longitudinal myocyte orientation; angulated intrusion of superficial myocytes toward the endocardium</td>
</tr>
<tr>
<td>Physiological pump conditions</td>
<td>High-resistance, high pressure pump; dominant radial thickening and contraction during ejection</td>
<td>Low-resistance, low-capacitance pump; peristaltic-like motion from inflow to outflow during ejection</td>
</tr>
<tr>
<td>Flow characteristics</td>
<td>Well-defined isovolumic contraction and relaxation; no hangout period</td>
<td>No or minimal isovolumic periods; hangout period</td>
</tr>
</tbody>
</table>
These physiological changes are mirrored by changes in myocardial contraction patterns. The systemic RV demonstrates increased circumferential contraction relative to decreased longitudinal shortening in a pattern indistinguishable from the normal LV. This observation is somewhat surprising in that diffusion tensor magnetic resonance imaging shows that fiber orientation in RV hypertrophy is not fundamentally different from normal. Likewise, the functionally single systemic RV in hypoplastic left heart syndrome may adapt a more circumferential versus longitudinal contraction pattern after stage 1 of surgical palliation (a particularly vulnerable period for these patients). Yet, the RV in hypoplastic left heart syndrome continuously faces systemic resistance from fetal through postnatal life, and it is difficult to attribute changes in RV contraction patterns to increased afterload alone.

At a molecular level, recent literature has highlighted differences between the RV and LV in the expression of genes involved in the response to pressure loading and failure. Some of these differences are detailed in the following text and are summarized in Table 2. Likewise, there are differences in the RV response to certain effectors, including adrenergic hormones. Although α-adrenergic agonists increase LV contractility, they may decrease RV contractility. Long-term infusion of norepinephrine induces LV but not RV hypertrophy.

In response to increased afterload, the RV reverts to a fetal gene pattern, re-expressing genes normally expressed in the fetal but not postnatal RV. This includes a shift from α- to β-myosin heavy chain expression and an increase in adrenergic receptors, calcineurin activation, and phosphodiesterase type-5 expression. A detailed analysis of the accumulating experimental literature on the progression from adaptive to maladaptive hypertrophy and from hypertrophy to failure is beyond the scope of this review. However, suffice it to say that not all studies of RV afterload show RV failure. One study in rodents found that progressive pulmonary artery banding induces RV hypertrophy but not failure, as evidenced by increased contractility; although RV pressure was at only ~60% of systemic levels, a degree of severity that usually does not induce symptoms in patients with pulmonary stenosis. Although it is clear that pressure overload alone does not induce RV failure, and even if contractility increases as an adaptive response to increased afterload, RV stroke volume and cardiac output may still decrease, fulfilling the definition of failure for some. Other rodent studies inducing systemic RV pressure have shown RV failure, RV dilation, decreased RV wall motion, elevated RV end-diastolic pressure, decreased cardiac output, clinical right heart failure, and decreased survival.

Microarray gene chip studies of mice with LV hypertrophy from aortic banding compared with mice with RV hypertrophy from pulmonary banding have demonstrated both similar and different LV and RV adaptive mechanisms. One pathway more activated in the pressure-loaded RV compared with the pressure-loaded LV is the Wnt pathway. Wnt regulates glycogen synthase kinase-3b activity, a serine/threonine protein kinase active in multiple intracellular signaling pathways, including cell proliferation, migration, inflammation, glucose regulation, and apoptosis. Therefore, there are potentially multiple differences between the RV and LV in their adaptation to increased loading and potential differences in metabolism, mitochondrial remodeling, and glycolysis-glucose oxidation coupling. These metabolic changes may subsequently lead to hyperpolarization of the mitochondrial membrane potential in RV hypertrophy, inefficient energy metabolism, and increased lactate production at an earlier stage of maladaptation compared with the LV. These molecular effects have potential therapeutic implications specific for the pressure-loaded RV. For example, dichloroacetate,
In increased volume loading, the RV appears more prone than the LV to developing fibrosis, as demonstrated in an experimental pig model with an aortocaval shunt. Similarly, patients after surgical repair of tetralogy of Fallot who have long-standing RV volume load secondary to pulmonary insufficiency develop RV fibrosis, even remote from surgical incision sites. This is clinically important as a risk factor for long-standing RV volume load secondary to pulmonary insufficiency develop RV fibrosis, even remote from surgical incision sites. It has been suggested that these differences in response between the RV and LV to volume loading may stem from the different embryological origin of the 2 ventricles. 

There has been increasing interest in the role of microRNAs (miRNA) as regulators of a wide range of cardiovascular processes and as possible therapeutic targets. Studies have highlighted both overlapping and varying expression between the failing RV and LV in various transcription factors, mRNA, and miRNA expression. Some transcription factors such as Iroquois homeobox 2 are expressed in the LV but not the RV. Others, including some nuclear receptors and insulin growth factor-1, are expressed in both ventricles but to different degrees. The lack of Iroquois homeobox 2 in the normal RV may explain why atrial natriuretic peptide is not expressed in normal RV. Failing RVs from rodents with SU5416/ hypoxia-induced PAH show overall increased miRNA but a specific decrease in miRNA 133a. miRNA 133a is thought to suppress cardiac fibrosis and is decreased in the failing LV secondary to aortic constriction. This aligns with the marked upregulation of connective tissue growth factor/CCN2 and other profibrotic signaling molecules during RV and LV fibrosis in our and other models of RV afterload and failure. In contrast, miRNA 21 and 34c* may increase during LV failure but decrease in RV failure. Reddy et al investigated miRNAs during the transition from RV hypertrophy to RV failure and compared these with miRNA expression in LV hypertrophy or failure. During RV hypertrophy, there was altered expression of miRNAs 199a-3p, which is associated with cardiomyocyte survival and growth. With the progression to RV failure and reactivation of the fetal gene program, there was increased expression of miRNA 208b, as well as miRNA 34, miRNA 21, and miRNA 1, which are associated with apoptosis and fibrosis. These patterns of miRNA expression are largely similar to LV hypertrophy and failure. However, there were several notable differences between RV and LV miRNAs linked to cell survival, proliferation, metabolism, extracellular matrix turnover, and impaired proteasomal function (miRNA 28, miRNA 148a, and miRNA 93), which were upregulated in RV hypertrophy or failure and downregulated or unchanged in LV hypertrophy or failure. Similarly, these investigators found that although the molecular responses of the RV and LV to increased afterload are mostly concordant, several key transcripts are increased in the afterloaded RV but not in the afterloaded LV. These included clusterin, neuroblastoma suppression of tumorigenicity 1, Dkk3, Sfrp2, formin binding protein, annexin A7, and lysyl oxidase. From these studies, it seems that although the ventricles share many common response mechanisms to stress, several key differences may warrant different management strategies in ventricular hypertrophy and the progression to failure. A better understanding of these subcellular events may lead to the development of more effective therapies for RV failure.

### Table 2: Molecular Differences Between the Left and Right Ventricles in Response to Adverse Loading

<table>
<thead>
<tr>
<th>Molecular Response</th>
<th>Right Ventricle</th>
<th>Left Ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wnt pathway activation and glycolysis-to-glucose oxidation metabolism in afterload</td>
<td>Higher activation; potentially inefficient energy metabolism</td>
<td>Lower activation; potentially improved energy metabolism</td>
</tr>
<tr>
<td>Fibrotic response to volume loading</td>
<td>Stronger</td>
<td>Weaker</td>
</tr>
<tr>
<td>Irx2 transcription factor expression in afterload</td>
<td>Not expressed</td>
<td>Expressed</td>
</tr>
<tr>
<td>Atrial natriuretic peptide expression</td>
<td>Not expressed</td>
<td>Expressed</td>
</tr>
<tr>
<td>miRNA 133a expression in experimental PAH</td>
<td>Increased</td>
<td>Not increased</td>
</tr>
<tr>
<td>Expression in afterload of clusterin, neuroblastoma suppression of tumorigenicity 1, Dkk3, Sfrp2, formin binding protein, annexin A7, lysyl oxidase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to α-1 adrenergic receptor agonists</td>
<td>Decrease contractility</td>
<td>Increase contractility</td>
</tr>
<tr>
<td>Response to long-term norepinephrine infusion</td>
<td>No hypertrophy</td>
<td>Hypertrophy</td>
</tr>
<tr>
<td>miRNA 28, 148a, and 93 expression in failure</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Response to dichloroacetate in hypertrophy</td>
<td>Increased inotropy</td>
<td>Unchanged inotropy</td>
</tr>
<tr>
<td>Response to PDE5 inhibitors in hypertrophy</td>
<td>Increased inotropy</td>
<td>Unchanged inotropy</td>
</tr>
<tr>
<td>Response to recombinant BNP infusion</td>
<td>Unchanged inotropy</td>
<td>Increased inotropy</td>
</tr>
</tbody>
</table>

BNP indicates brain natriuretic peptide; Iroquois homeobox 2; miRNA, microRNA; PAH, pulmonary arterial hypertension; and PDE5, phosphodiesterase type-5.

*See text for details.
novel, ventricle-specific treatments. Inhibition of miRNA 208a has recently been shown to abrogate LV dysfunction in rodent models of LV failure49; similar responses, albeit targeted toward a different miRNA signature, might be anticipated for RV failure.

Are the RV and LV Really Different?

Although there are undoubtedly differences in RV and LV responses to adverse loading and differences in response of the more complex heart failure syndrome to various therapies, it is also evident that the 2 ventricles share many common features in response to adverse loading and failure. The fetal gene pattern shift, particularly the myosin heavy chain shift from the α to β isoform, a hallmark of fetal gene reactivation, is also triggered in LV failure.35 Likewise, the progression from compensated to decompensated hypertrophy occurs in both ventricles. Common findings in both RV and LV hypertrophy are collagen deposition, fibrosis, and extracellular matrix remodeling.51 The mechanisms inducing fibrosis are multiple, and in the setting of increased ventricular afterload, putative triggers may include regional ischemia, necrosis, and apoptosis, among others.52 Our own experimental data suggest common injury pathways in both ventricles. In response to isolated RV afterload induced by pulmonary artery banding in a rabbit model, we found RV and LV fibrosis and upregulation of transforming growth factor-β1 signaling in both ventricles (Figure 4). Just as RV fibrosis is commonly seen in the setting of both severe RV afterload and chronic pulmonary regurgitation, LV fibrosis is common in both aortic stenosis and regurgitation.44,53,54 Pharmacological agents that decrease either pulmonary vascular resistance or systemic vascular resistance may attenuate the progression of fibrosis in the RV and LV, respectively. Likewise, mechanical unloading of the LV by LV assist devices can attenuate fibrosis in both ventricles.55 Microarray studies of thousands of genes have shown that although the RV response to pressure-induced hypertrophy is characterized by a stronger transcriptional response compared with the LV, there was no evidence of qualitatively distinct regulatory pathways in the RV compared with the LV.56

Mechanical and Functional Interdependence Between the RV and LV

Although it has been customary to consider LV function and RV function as separate entities, this approach is flawed. The ventricles share common injury mechanisms and anatomically share fibers that encircle both ventricles. They are intimately attached through a common septum and share the pericardial space (Figure 5).57-60 Consequently, the function of the 2 ventricles is inextricably linked in both the structurally normal and abnormal heart.

The importance of LV-to-RV myocardial cross-talk was elegantly demonstrated in an experimental study of intact explanted hearts in which electric but not mechanical continuity between the RV and LV was interrupted.61 RV pacing led to little detectable mechanical activity (measured as developed pressure) in the LV. Conversely, however, pacing-induced contraction of the electrically isolated LV was associated with the development of an almost normal RV pressure trace and pulmonary blood flow.61 Santamore et al62 further elucidated the individual effects of LV volume loading and dysfunction on RV developed pressure. Reducing LV volume from its optimal volume to zero caused a 5.7% decrease in RV developed pressure, whereas ligating the coronary supply to the LV free wall resulted in an additional 9.3% decrease in RV developed pressure. Cutting the LV free wall to prevent any developed LV free wall force caused a further 45% decrease in RV developed pressure. Changes in RV developed pressure resulting from changes in LV volume and from coronary occlusion correlated with the degree of septal bulging into the RV cavity during systole, suggesting that the septum plays an important role in RV function.

Figure 4. Representative sections showing Masson trichrome staining for collagen content. The bar graph of the quantitative analysis shows increased collagen in response to pulmonary arterial banding (PAB) in both the right ventricle (RV) and the left ventricle. In association with increased fibrosis, there is upregulation of profibrotic signaling molecules, including transforming growth factor-β (TGFβ), connective tissue growth factor (CTGF), and matrix metalloproteinases (MMP) 2 and 9.49
role in mediating ventricular-ventricular interactions. From these experiments, it was estimated that >50% of the normal RV mechanical work may be generated by LV contraction and that the LV free wall plays a pivotal role in RV function. Similarly, LV isovolumetric contraction results in simultaneous increases in RV stroke volume and developed pressure for a constant RV volume. Hoffman et al. expanded on these observations in in vivo experiments. By replacing the RV myocardium with a noncontractile prosthesis, they were able to show virtually normal RV pressure generation as a consequence of normal LV shortening. Just as interesting was the observation that intact RV geometry is crucial for normal LV mechanical performance. During gradual enlargement of the noncontractile RV free wall, there was a progressive reduction in both RV and LV mechanical work; that is, as the RV dilated, LV pressure development and stroke work decreased. These experimental phenomena have been shown in vivo in the human heart during pre-excitation of 1 ventricle by pacing or during extrasystolic beats. Normally, LV electric activation and RV electric activation are temporally close enough that it is difficult to separate the peak dP/dt spike of 1 ventricle from the other. When LV activation is sufficiently separated from RV activation by a ventricular extrasystole or by left bundle-branch block, the contribution of LV contraction to RV dP/dt becomes apparent.

The RV also profoundly affects LV performance. Changes in RV volume lead to substantial changes in load-independent measures of LV function and a shift in the LV pressure-volume relation. These effects may be clinically relevant when the RV is volume unloaded by placement of a caval pulmonary shunt. Danton et al. showed experimentally that acute RV ischemia induced by coronary artery ligation induced LV dysfunction as measured by end-systolic elastance, a load-independent measure of LV contractility. LV dysfunction secondary to RV ischemia was reversed by the addition of a caval pulmonary shunt with restoration of LV end-systolic elastance. These load-independent effects on LV contractility were likely mediated by the caval pulmonary shunt relieving RV volume load, thereby limiting RV dilation and restoring LV cavity geometry. One may envisage similar effects on LV function in the clinical setting of various congenital heart disease lesions, for example, when a caval pulmonary shunt is placed as part of a “1.5-ventricle repair” for RV hypoplasia or dysfunction.

In PAH, in addition to decreased cardiac output that results directly from RV failure, leftward displacement of the interventricular septum impedes LV filling (Figure 6). This secondary LV geometric change is linearly related to cardiac output, whereas RV end-diastolic volume, in and of itself, is not related to cardiac output. Similarly, in patients with tetralogy of Fallot and conduit stenosis, the prolonged septal shift induced by RV afterload and prolonged RV contraction leads to reduced LV filling as the septum bulges into the LV in diastole. Relief of conduit stenosis reverses septal curvature, shortens RV contraction, synchronizes LV and RV contraction and relaxation, improves LV filling, and improves exercise capacity. The LV eccentricity index, a simple echocardiographic index that quantifies the anterior-posterior LV compression by the distended RV, correlates with survival in adults with PAH. Similarly, we have found...
systolic to diastolic duration.78 from clinical worsening, lung transplantation, or death from the time of the first echocardiogram is worse in children with a higher ratio of right ventricular output and leads to adverse ventricular-ventricular interactions by limiting left ventricular preload. These adverse ventricular interactions translate into worse survival in children with pulmonary arterial hypertension, as shown by Kaplan-Meier survival analysis of 47 children with pulmonary arterial hypertension stratified by the ratio of systolic to diastolic duration. The percent of children free from clinical worsening, lung transplantation, or death from the time of the first echocardiogram is worse in children with a higher ratio of systolic to diastolic duration.78

Concomitantly, available RV filling time (ie, diastolic duration) is severely shortened,77 compromising RV and LV filling and the ratio of RV systolic to diastolic duration are linked to clinical outcome.78,79 At the basis of these relations is a prolongation of RV systole, extending into LV diastole, an adverse interaction worsened by increasing heart rate. Concomitantly, available RV filling time (ie, diastolic duration) is severely shortened,77 compromising RV and LV filling and filling rate.86,89 This can be summarized as an increase in overall systolic time but a truncated RV ejection time and a significant decrease in filling time. The shortened ejection time and reduced stroke volume secondary to increased afterload further contribute to decreased LV filling and cardiac output.80 In children with PAH, there is a marked logarithmic decrease in diastolic duration and increase in the ratio of systolic to diastolic duration when heart rate increases compared with control subjects.78 We have shown that the ratio of systolic to diastolic duration, measured from the duration of tricuspid regurgitation Doppler in a patient with pulmonary hypertension, is markedly longer than diastole. This demonstrates prolonged contraction and shortened filling time of the right ventricle, which impairs right ventricular output and leads to adverse ventricular-ventricular interactions by limiting left ventricular preload. These adverse ventricular interactions translate into worse survival in children with pulmonary arterial hypertension, as shown by Kaplan-Meier survival analysis of 47 children with pulmonary arterial hypertension stratified by the ratio of systolic to diastolic duration. The percent of children free from clinical worsening, lung transplantation, or death from the time of the first echocardiogram is worse in children with a higher ratio of systolic to diastolic duration.78

The ratio of systolic (S) to diastolic (D) duration as measured from tricuspid valve regurgitation Doppler in a patient with pulmonary hypertension. In contrast to the normal situation in which diastolic duration is equal to or longer than systolic duration, systole is markedly longer than diastole. This demonstrates prolonged contraction and shortened filling time of the right ventricle, which impairs right ventricular output and leads to adverse ventricular-ventricular interactions by limiting left ventricular preload. These adverse ventricular interactions translate into worse survival in children with pulmonary arterial hypertension, as shown by Kaplan-Meier survival analysis of 47 children with pulmonary arterial hypertension stratified by the ratio of systolic to diastolic duration. The percent of children free from clinical worsening, lung transplantation, or death from the time of the first echocardiogram is worse in children with a higher ratio of systolic to diastolic duration.78

Figure 7. A. The ratio of systolic (S) to diastolic (D) duration as measured from tricuspid valve regurgitation Doppler in a patient with pulmonary hypertension. In contrast to the normal situation in which diastolic duration is equal to or longer than systolic duration, systole is markedly longer than diastole. This demonstrates prolonged contraction and shortened filling time of the right ventricle, which impairs right ventricular output and leads to adverse ventricular-ventricular interactions by limiting left ventricular preload. These adverse ventricular interactions translate into worse survival in children with pulmonary arterial hypertension, as shown by Kaplan-Meier survival analysis of 47 children with pulmonary arterial hypertension stratified by the ratio of systolic to diastolic duration. The percent of children free from clinical worsening, lung transplantation, or death from the time of the first echocardiogram is worse in children with a higher ratio of systolic to diastolic duration.78
but also to reduced load-independent indexes of LV contractility. This change in LV volume was obviated by release of the pericardium, with a similar degree of RV dilation but a nonsignificant decrease in LV volume. However, acute RV dilation under these circumstances was still associated with a significant decrease in load-independent measures of LV myocardial contractility. This could not be explained by changes in LV geometry and almost certainly reflected abnormalities of myocardial cross-talk under the circumstances of acute RV dilation. Therefore, although septal shift in the setting of a relatively noncompliant pericardium is a crucial factor in mediating ventricular interactions, myocardial cross-talk is another major component and likely occurs as a result of the presence of common myocardial tracts or fibers shared by both ventricles, especially in the superficial layers. As demonstrated elegantly in pathological specimens and by diffusion tensor magnetic resonance imaging studies, these myofiber tracts originate predominantly in the superficial layer of the LV and cross to the RV (Figure 5). As for the LV, the aggregated RV myocytes form helical angles and intrude in the oblique orientation from the epicardial to endocardial layers.

In response to afterload, the hypertrophied RV maintains this basic structure and does not form an extensive layer of circular myocytes, which may explain the previously discussed shift from a longitudinal to circumferential strain pattern.

Although shared myofibers likely play a role in mediating adverse ventricular-ventricular interactions, they may also constitute a target for therapeutic intervention. We have developed a rabbit model of sustained increased RV afterload using adjustable pulmonary artery banding. This model allows study of isolated increased RV afterload on the LV without potential confounding effects of pharmacological agents or hypoxia often used in animal PAH models. We found that both acute and chronic isolated RV afterload induced by pulmonary artery banding leads to not only RV but also LV global dysfunction. The functional compromise is accompanied in both ventricles by adverse remodeling as manifested by biventricular myocyte hypertrophy, reduced contractility, and increased fibrosis. Although RV hypertrophy is an expected finding secondary to isolated RV afterload, the similar findings in the otherwise healthy LV are intriguing. We further demonstrated that under these circumstances of isolated RV afterload, the addition of mildly increasing LV afterload by systemic epinephrine or norepinephrine in acute RV failure (suggesting that systemic vasoconstriction might be a viable strategy for the treatment of acute LV failure when LV function is well preserved) or by the addition of mild aortic banding in both acute and chronic RV afterload leads to an increase in load-independent indexes of LV and RV contractility. These findings extend the work of Belenkie et al., who demonstrated that aortic constriction during acute RV afterload leads to increased stroke volume independently of right coronary artery flow. Perhaps more clinically relevant was our observation of maladaptive fibrotic responses in both ventricles after isolated RV afterload associated with upregulation of genes classically involved in mediating fibrosis, including transforming growth factor-β1, connective tissue growth factor, and endothelin-1 in both ventricles. Likewise, in both ventricles, isolated RV afterload was associated with extracellular matrix degeneration expressed by upregulation of matrix metalloproteinases. Conversely, the observed improvement in LV and RV contractility induced by the addition of mild LV afterload was associated with amelioration of biventricular myocyte hypertrophy and fibrosis and downregulation of fibrosis signaling. Using a similar juvenile rabbit model of pulmonary artery banding, Kitahori et al. found septal apoptosis, fibrosis, and reduced capillary density after 6 to 8 weeks of pulmonary artery banding that extended to the LV free wall. Visner et al. demonstrated in dogs that impaired LV systolic function during acute RV hypertension induced by pulmonary artery constriction was accounted for by rearrangements in LV dynamic geometry that resulted primarily from the anatomic contiguity of the 2 ventricles at the septal insertion points. Septal shift is determined predominantly by the transseptal pressure gradient. Therefore, in the hypertensive RV, not only is septal function impaired, but the configuration of the displaced septum into the LV may increase local wall shear stress and regional injury. Indeed, the RV septal insertion regions may be particularly prone to increased stress and subsequent fibrosis as they are exposed to high shear forces from LV circumferential and RV longitudinal shortening. Magnetic resonance imaging delayed gadolinium enhancement, thought to represent fibrosis, at the RV septal insertion points has been found almost universally in adult patients with PAH and is in direct relation to the degree of RV afterload. Fibrosis at the RV septal insertions was associated with reduced RV longitudinal contraction, and the extent of RV fibrosis in PAH has been inversely related to RV ejection fraction, stroke volume, and end-systolic volume and to increased mortality. The improvement seen in RV and LV function with the addition of a mild aortic band in our rabbit model may stem from amelioration of the septal shift induced by the aortic band, by improvement in ventricular geometry, and by inducing...
increased LV contractility through a modest increase in LV afterload. This in turn may lead to increased RV contractility through shared myofibers. Recently, we have demonstrated in our rabbit model that angiotensin receptor blockade can lead to similar effects with a reduction in biventricular fibrosis and its signaling.102

In clinical practice, increasing the subpulmonary LV afterload to improve cardiac function is used in patients who have congenitally corrected transposition of the great arteries and tricuspid regurgitation. In this condition, the RV is the systemic ventricle, and the systemically positioned tricuspid valve is often anatomically abnormal and regurgitant.17 The septum of the dilated systemic RV bulges toward the LV, carrying with it the tensor apparatus of the tricuspid valve, leading to a vicious spiral of tricuspid regurgitation and RV dilation. By placement of a controlled pulmonary band to increase LV afterload on the one hand while avoiding LV failure on the other, the septum shifts toward the LV and assumes a more neutral position, thereby changing the tricuspid valve annular configuration and reducing tricuspid regurgitation. It is interesting to postulate whether pulmonary artery banding in this situation increases LV contractility, thereby leading to an increase in systemic RV contractility through shared myocardial fibers, as we hypothesized for the addition of aortic cross-talk may be important to ventricular mechanics when they fail. Whether a number of key differences in their molecular response to failure will provide a potential platform for RV specific intervention remains to be seen. Furthermore, ventricular-ventricular interactions are important to cardiac function in both physiology and disease. Through shared myocardial fibers, the interventricular septum and the common pericardium, LV contraction contributes to RV pressure development, and RV loading affects LV function. Targeting pathways specific to the stressed or failing RV, pathways that are common to both ventricles, and targeting the interactions between the ventricles may ultimately lead to novel therapies to treat RV and LV failure.

**Disclosures**

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