Right–Left Ventricular Interactions in RV Afterload and Preload

6

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Abstract

Ventricular–ventricular interactions refer to the cumulative effect of changes in filling, function, geometry and synchrony of one ventricle on the filling, function, geometry and synchrony of the contra-lateral ventricle. A substantial portion of RV mechanical work under normal circumstances is generated by LV contraction. However, the RV also profoundly influences LV function. These RV to LV and LV to RV interactions, are particularly prominent during increased volume and pressure loading, and affect disease course and outcome. These ventricular–ventricular interactions may also be recruited and targeted for therapeutic benefit. For example, controlled pulmonary artery banding in dilated cardiomyopathy and aortic banding in pulmonary hypertension may augment the function of the failing left and right ventricle respectively. Even in single ventricle physiology, the hypoplastic ventricle can affect the function of the dominant ventricle. In this chapter we review the physiology, pathophysiology and therapeutic benefit of ventricular–ventricular interactions.

Keywords

Ventricular–ventricular interactions • Pulmonary hypertension • Systole Diastole

Introduction

Considerable emphasis has been placed on differentiating between the embryological origins, characteristics, physiology and function of the left (LV) and right (RV) ventricles. However, far less emphasis has been placed on the intimate relations between the two sides of the heart. Yet, these reciprocal relations form an innate and fundamental

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basis for cardiac function in both physiology and disease. Ventricular–ventricular interactions (VVI) refer to the cumulative effect of changes in filling, function, geometry and synchrony of one ventricle on the filling, function, geometry and synchrony of the contra-lateral ventricle. In this chapter we will review the physiology of VVI and provide examples of how they affect cardiac function in specific conditions; and how they may possibly be utilized for therapeutic benefit.

The Physiological Basis of Ventricular–Ventricular Interactions

The RV and LV are intimately attached through a common septum, a common pericardial space and shared myocardial fibers encircling the ventricles [1]. Santamore's laboratory made pivotal discoveries regarding the effects of LV volume loading and dysfunction on RV developed pressure. A decrease in LV volume below its optimal volume caused a 6% decrease in RV developed pressure. LV free wall ischaemia/infarction from coronary artery ligation resulted in an additional 9% decrease in RV developed pressure. In the absence of any LV free wall force development (caused by LV free wall incision), there was a dramatic 45% additional decrease in RV developed pressure [2]. Thus, it appears that a substantial portion of RV mechanical work under normal circumstances is generated by LV contraction and that the LV free wall plays a major role in RV function [2]. In fact, Hoffman demonstrated that even when the RV myocardium is entirely replaced with a non-contractile prosthesis, normal LV shortening lead to virtually normal RV pressure generation [3]. However, these experiments also demonstrated that VVI operate not only from left to right, but also from right to left; and that intact RV geometry is necessary for normal LV function. Progressive enlargement of the non-contractile RV, lead to a progressive reduction in both RV and LV mechanical work [3]. Thus, progressive RV dilatation lead to reduced LV pressure development and stroke work [3].

From Santamore's classic experiments, not only was intact LV free wall function an important contributor to RV function, but at the same time, changes in RV developed pressure were related to septal position, particularly septal bulging into the RV cavity during systole, suggesting an important role for the septum in mediating ventricular–ventricular interactions [3]. While these findings may suggest that changes in RV volume are the cause of decreased RV developed pressure, Shertz showed that even when RV volume is held constant, LV isovolumetric contraction results in simultaneous increases in RV stroke volume and RV developed pressure [4]. Therefore, it seems that additional mechanisms are at play, beyond RV volume and septal shift alone.

These additional mechanisms were also vividly delineated by Santamore's group. In an experimental model of intact but explanted hearts, the investigators disrupted electrical but not mechanical continuity between the RV and LV (Table 6.1) [5]. Thus electrical stimulation of the LV would only lead to LV contraction, and

Table 6.1 Mechanisms of ventricular–ventricular interactions

Mechanism	Pathophysiology	Example
Septal position	Septal displacement reduces contralateral ventricular volume and geometry	LV compression in PAH
Pericardial constraint	Enhances septal displacement mechanism by limiting available space	Tamponade physiology
Shared myofibers	Fibers in the superficial layer traverse both ventricles	Presumed mechanism whereby pulmonary artery band enhances LV function in DCM
Coronary circulation	In some conditions, LV function is dependent on coronary flow originating from the RV cavity through 'sinusoids'	Pulmonary atresia/intact ventricular septum

electrical stimulation of the RV would only lead to LV contraction. This allowed study of the effects of the contraction of one ventricle on developed pressure and flow in the contralateral ventricle. In these experiments, during RV pacing, there was minimal developed pressure in the LV. Conversely, during pacing of the electrically isolated LV, RV pressure development and pulmonary blood flow were almost normal [6]. These ex vivo experimental observations have been elegantly shown in the human heart in vivo during pre-excitation of one ventricle by pacing or during extra-systolic beats [6]. Under normal circumstances, LV and RV electrical activation occur almost simultaneously (with a very short delay) and when measuring developed pressure over time (dP/dT) in either ventricle, only one pressure spike is observed. This makes it difficult to tease out the separate contributions of the contraction of one ventricle to developed pressure in the contralateral ventricle. However, when the LV is activated separately from the RV, by an extra-systolic beat or by left bundle branch block, two distinct pressure spikes can be observed in the RV, one that arises from RV contraction and the other that arises from LV contraction [6].

Up to now, we have emphasized the impact of LV function on the RV. However, the RV also influences LV function. These RV to LV interactions have been shown both during increased RV volume loading, as well as during increased RV pressure loading. We already discussed Hoffman's experiments where a progressively enlarging (even though non-contractile) RV, adversely impacted LV developed pressure [3]. Indeed, during changes in RV volume loading, there can be substantial changes in LV function and even LV contractility, as manifested by a shift in the end systolic pressure-volume relation [7]. How important these effects are in the clinical setting requires further study. In experimental models of acute RV ischemia, which leads to acute RV dysfunction and dilatation; LV dysfunction and reduced contractility is observed [8]. This dysfunction can be reversed by volume-unloading the RV using a superior vena cava to pulmonary artery shunt with disconnection of the PA from the RV. However, the question arises: How does volume unloading the dysfunctional RV, lead to improvement in load-*independent* parameters of LV contractility?

Changes in LV volumes alone following RV dysfunction and acute dilatation may not adequately account for all these effects. During acute right coronary ischemia and RV dilation, there was a decrease in LV size mediated primarily by a leftward septal shift secondary to RV dilatation [9]. However, this was accompanied by reduced LV contractility measured by load-independent indices, which are not influenced by ventricular volumes [9]. Moreover, when pericardial constraint was relieved by opening the pericardium, there was no significant change in LV volume or RV dilation, but an observed improvement of load-independent measures of LV myocardial contractility.

One explanation for these findings is that decreasing RV volume, improving RV dilation or reversing leftward septal shift all improve or restore LV geometry thereby allowing improved myocardial mechanics and contractility [8]. Nonetheless, while septal shift and a non-compliant pericardium are central mediators of right to left ventricular interactions, the load independent nature of LV measures in the experiments described above suggests that changes in LV geometry do not sufficiently account for its improved contractility [10].

An additional explanation for the observed phenomena is through the muscle fibers themselves. It has been well established that there are common muscle tracts that transverse the LV and RV in the superficial and mid layers [11, 12]. An increase in LV contractility for example, may therefore lead to an increase in RV contractility, presumably through the Anrep effect. This concept was demonstrated by Belinkie et al. who demonstrated that acute aortic constriction leads to improvement in the performance and stroke volume of the failing RV, independent of changes in right coronary artery flow [13]. The authors attributed the ventricular–ventricular interactions, at least in part, to a rightward septal shift and change in the inter-ventricular pressure gradient brought about by aortic constriction [13]. We have recently expanded on these concepts as a

possible therapeutic target in increased RV afterload and pulmonary arterial hypertension. However, before detailing these findings, let us first expand on the adverse ventricular–ventricular interactions in pulmonary hypertension and increased RV afterload.

Right to Left Ventricular–Ventricular Interactions in Increased RV Afterload

In patients with PAH, reduced LV filling is secondary to at least two important phenomena. Firstly, due to reduced RV stroke volume and output, LV preload is reduced. This has been demonstrated by Gurudevan et al. [14] before and after pulmonary embolectomy in patients with chronic thromboembolic pulmonary arterial hypertension. In those patients, pulmonary vein and mitral Doppler inflow patterns clearly improved after relief of the pulmonary obstruction. Concomitantly, RV hypertension and dilatation causes leftward displacement of the interventricular septum, which directly reduces LV filling [10, 15–19]. Following this, Gan et al. using MRI, demonstrated that LV end-diastolic volume, more than RV end-diastolic volume is linearly correlated to cardiac output [15]. These RV–LV interactions can be simply assessed using the LV eccentricity index [20, 21]. This is a simple echo index, measured from 2-D imaging which relates the lateral to anterior-posterior dimensions of the LV in the short-axis, thereby reflecting the degree of anterior-posterior LV compression by the distended RV. The importance of this interaction is supported by the finding that the LV eccentricity index is related to survival in PAH [20]. We have recently shown that in children with iPAH, that the LV eccentricity index is associated with death or need for lung transplantation [22]. Thus it seems that in increased RV afterload, the hypertensive RV affects LV geometry and function both in an in-series effect (reduced RV output leading to decreased LV preload); as well as a parallel effect arising from leftward septal shift.

These same ventricular–ventricular interactions were beautifully demonstrated using strain imaging by MRI in patients with tetralogy of Fallot who had outflow tract obstruction [23]. These investigators showed how prolonged leftward shift of the septum secondary to increased RV afterload leads to reduced LV filling when the septum bulges leftward in early LV diastole. Relief of the RV outflow obstruction reversed these findings, with normalization of septal curvature, shortening of RV contraction and improved LV filling [23]. Importantly, improved LV filling was directly related to an improvement in exercise capacity, demonstrating the clinical relevance of these findings [23].

However, the right to left adverse ventricular–ventricular interactions observed in increased RV afterload extend beyond altered geometry alone, and substantially affect myocardial health and performance. Visner 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 primarily resulted from the anatomic contiguity of the two ventricles at the septal insertion points [19]. Septal shift is predominantly determined by the transeptal 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 [17]. 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 [17, 24, 25]. Recently, MRI delayed gadolinium enhancement, thought to represent fibrosis, at the RV septal insertion points has been found almost universally in adult patients with PAH and correlates with the degree of RV afterload [24, 26, 27]. Fibrosis at the RV septal insertions was associated with reduced RV longitudinal contraction [27] and the extent RV fibrosis in PAH has been inversely related to RV ejection fraction, stroke volume and end-systolic volume; and also with increased mortality [24].

However, from the findings discussed above, and from our own work, it is apparent that it is not only the geometrical consequences of leftward septal shift that induces adverse ventricular interactions, but also the timing of these events.

Temporal Aspects of Adverse Ventricular–Ventricular Interactions in Increased RV Afterload

Not only is the interventricular septum shifted leftward towards the LV, reducing its filling and volume; but this leftward shift is prolonged due to the prolonged RV contraction time observed in PAH and increased RV afterload (Fig. 6.1). Although pulmonary ejection time is short in PAH [28], the duration of RV contraction is prolonged (Fig. 6.1) [29]. At the same time, RV diastole and filling time are shortened (Fig. 6.1) [28]. The prolonged RV systole, extends into the time period where the LV has already started its diastole, thereby compromising LV filling (Fig. 6.1) [7, 14, 15]. This adverse relation is worsened by increasing heart rate as diastole disproportionately shortens more than systole with increasing heart rate. Thus children with PAH have a marked decrease in diastolic duration and increase in the systolic duration when their heart rate increases as compared with controls [29]. The ratio between systolic and diastolic duration measured from tricuspid regurgitation Doppler, reflects the overall prolonged systolic duration and decreased LV filling (Fig. 6.1). We have shown the S:D ratio is temporally related to death or need for lung transplantation in the pediatric PAH population with the highest risk occurring when the S/D ratio was >1.40 [29].

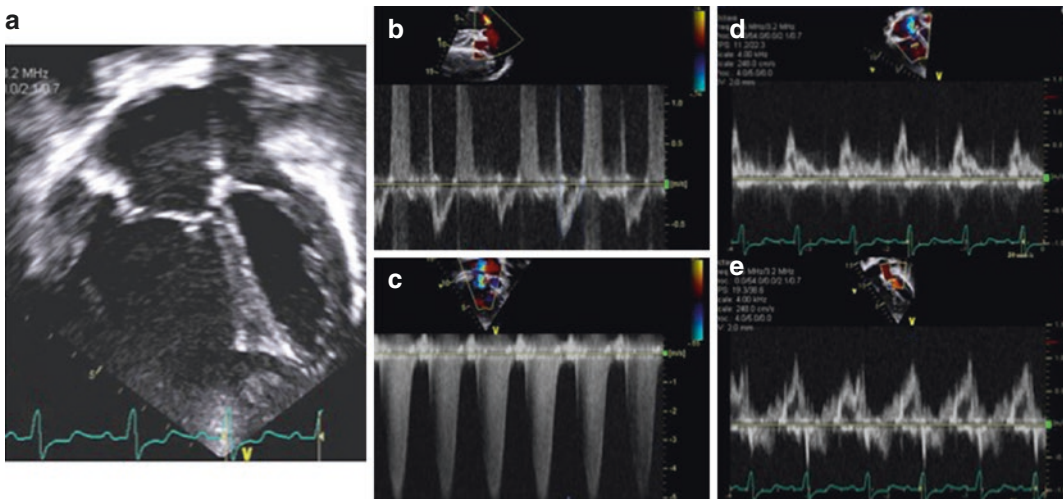

Fig. 6.1 Child with severe idiopathic pulmonary hypertension. Panel (**a**) depicts an apical 4-chamber view showing a markedly dilated right ventricle which compresses the left ventricle in systole and diastole. Panel (**b**) depicts Doppler in the pulmonary artery. Right ventricular ejection is short in duration and reducing volume due to severely increased pulmonary vascular resistance (Panel **b**). However, right ventricular contraction and systole, is actually prolonged as seen by the duration of tricuspid regurgitation (Panel **c**). Thus, Doppler of the tricuspid regurgitation jet is useful not only to measure right ventricular systolic pressure, but also the duration of systole (duration of the tricuspid regurgitation) and diastole (the duration of the interval between tricuspid regurgitation jets). The prolonged right ventricular systole shifts the septum leftward in left ventricular systole and diastole, thereby reflecting ventricular interactions whereby the displaced septum impedes left ventricular filling. Thus, not only is right ventricular diastolic filling compromised (Panel **d**) as seen by monophasic, late diastolic filling of short duration; but left ventricular diastolic filling is compromised as well with abnormal early (**e**) and late (**a**) filling relations occurring late (Panel **e**). Left ventricular diastolic filling is thus compromised by reduced right ventricular output (Panel **a**) and by prolonged right ventricular systole which shifts the septum leftward in left ventricular diastole (Panel **c**)

Thus, prolonged septal shift, reduced LV filling and a prolonged RV systolic to diastolic duration ratio are linked to clinical outcomes [29, 30]. The link between temporal and geometric events is further supported by the inverse relationship between heart rate and LV end-diastolic volume.

Adverse Right to Left Ventricular–Ventricular Interactions in Repaired Tetralogy of Fallot

Interventricular dyssynchrony contributes to prolonged RV contraction in PAH and is also important in other congenital heart disease such as tetralogy of Fallot (TOF) [31], where the delay between left and right isovolumic contraction time, is related to risk of ventricular arrhythmias and also to the patient's exercise capacity [32].

However, interventricular contraction delays are not the only adverse ventricular–ventricular interaction found in tetralogy of Fallot. Several studies have found linear relations between RV and LV systolic indices whether measured by ejection fraction, annular displacement or myocardial strain [33, 34]. Indeed, while TOF is most commonly considered a disorder predominantly affecting RV function, our group and others have shown that not only RV, but also LV myocardial strain is reduced in this population [35, 36]. Investigators from the Toronto General Hospital were among the first to demonstrate reduced LV myocardial strain in adults with more advanced and long-standing RV remodeling and dysfunction, while our group has demonstrated that reduced LV strain, as well as abnormal LV rotation mechanics, are already impaired in children, much earlier in the clinical course after surgical repair of TOF [35, 36]. Impaired LV dysfunction was related to the degree of RV enlargement and dysfunction, suggesting adverse ventricular–ventricular interactions [36, 37]. This is at least in part related to the presence of pulmonary regurgitation as pulmonary valve replacement leads not only to improved RV size and function but also to improved LV function [38, 39].

Findings of impaired LV dysfunction, whether at the myocardial or ventricular level is important as LV dysfunction has been found not only to be prevalent in the TOF population, but to be an important risk factor for functional impairment and even mortality [40]. We also found that not only RV but also LV incoordinate motion is worsened during exercise in children after TOF repair, suggesting that worsening of adverse interactions may be provoked by exercise [41].

While in the current discussion we have concentrated mainly on LV dysfunction in conditions predominantly affecting the RV, RV dysfunction is also apparent in diseases affecting predominantly the LV. PAH secondary to LV dysfunction or left sided obstructive lesions is an obvious example [42]. In LV DCM, concomitant RV dysfunction is a well-recognized risk factor for worse mortality [43]. We have also investigated more subtle examples of adverse left to right ventricular–ventricular interactions. For example, in aortic stenosis, we found reduced RV myocardial strain in a sub-set of patients [44]. In those patients with reduced RV myocardial function during aortic stenosis, RV strain improved after aortic valvuloplasty.

However, relief of valvar stenosis does not automatically lead to improvements in contralateral ventricular function. Li et al. found that following pulmonary valve balloon valvuloplasty for pulmonary stenosis, patients demonstrated persistent LV abnormalities including reduced myocardial strain and increased mechanical dyssynchrony at a mean interval of 18 ± 6 years after the procedure [45]. However, these LV abnormalities, were likely related to persistent RV abnormalities as these patients had larger RV volumes which correlated with the degree of decreased LV circumferential strain and increased dyssynchrony.

Additionally, there are situations where relief of RV afterload may lead to LV dysfunction. One classic example is in pulmonary atresia with intact ventricular septum where in a subset of patients LV myocardial coronary blood supply is dependent on the presence of coronary sinusoids. When LV coronary supply is compromised (e.g when the left coronary system is stenosed), LV coronary supply is dependent on collateral flow originating from the high-pressured, small, RV

cavity, through the sinusoids. In this situation decompressing the RV by opening the atretic RV outflow tract can lead to serious LV ischaemia and compromise. The presence of these sinusoids, even without RV dependence, may be associated with long-term risk for LV regional wall motion abnormalities, dysfunction and possibly increased risk for death [46]. This complex subject is well beyond the scope of this chapter, but demonstrates that coronary abnormalities and even differential RV to LV filling pressures, which affect coronary resistance and flow, can affect ventricular–ventricular interactions [47].

Using Ventricular–Ventricular Interactions for Therapeutic Benefit

Up to now, we have described several examples of adverse ventricular–ventricular interactions. Although shared myofibers and septal position play a role in mediating adverse ventricular–ventricular interactions they 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 systemic pharmacological agents or hypoxia often used in animal models of PAH. We found that both acute and chronic isolated RV afterload induced by pulmonary artery banding leads to biventricular dysfunction [48–50]. The functional compromise was accompanied in both ventricles by adverse remodeling as manifested by biventricular myocyte hypertrophy, reduced contractility and increased fibrosis [48, 49]. While RV myocyte hypertrophy is an expected finding secondary to isolated RV afterload, similar developments in the otherwise healthy LV is intriguing. Using a similar juvenile rabbit model of pulmonary artery banding, Kitahori found septal apoptosis, fibrosis, and reduced capillary density after 6 to 8 weeks of PAB which extended to the LV free-wall [51]. Interestingly, these animal data are different to findings in human subjects with increased RV afterload secondary to pulmonary hypertension where LV atrophy was present [52]. Whether this is explained by increased apoptosis or other mechanisms requires further investigation.

We further demonstrated in our rabbit pulmonary artery band model, that during isolated acute RV failure, a small increase in LV afterload by systemic epinephrine or norepinephrine or by the addition of mild aortic banding lead to an increase in load-independent indices of LV and RV contractility [48, 49]. In both the RV and LV, collagen deposition following pulmonary artery banding was associated with activation of the fibrosis cascade including TGFβ1, CTGF and endothelin (ET)-1; as well as with upregulation of matrix metalloproteinases which mark increased extra-cellular matrix degeneration. Conversely, the observed improvement in LV and RV contractility induced by addition of mild LV afterload was also beneficial during chronic RV afterload, and was associated with amelioration of biventricular myocyte hypertrophy and fibrosis as well as downregulation of fibrosis signaling [48, 49].

The improvement seen in RV and LV function with addition of a mild aortic band in our rabbit model may stem from amelioration of septal shift induced by the aortic band, improvement in ventricular geometry and also by inducing increased LV contractility through a modest increase in LV afterload. This in turn may lead to increased RV contractility through shared myofibers traversing both ventricles.

In clinical practice, increasing the subpulmonary ventricle's afterload to improve cardiac function is used in patients who have congenitally corrected transposition of the great arteries and tricuspid regurgitation. In ccTGA, the RV is the systemic ventricle and the systemically positioned tricuspid valve is often anatomically abnormal and regurgitant [53]. In this situation, the dilated systemic RV bulges towards the LV, with the septum pulling the tricuspid attachments leftward contributing to tricuspid valve non-coaptation and regurgitation. RV annular dilatation and these geometric abnormalities feed a worsening cycle of tricuspid regurgitation and RV dilation. By placement of a controlled pulmonary band to increase LV afterload (and LV pressures)

on the one hand, while avoiding LV failure on the other, the septum shifts towards the LV and assumes a more neutral position thereby changing TV annular configuration and reducing TR. It is also 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 banding in our aforementioned rabbit model.

While we demonstrated, at least in animal models, that increasing LV afterload can be used to enhance RV performance, one may ask whether the RV can be utilized to support the failing LV. One of the most interesting initiatives addressing this idea was promoted by the Giessen group who investigated pulmonary artery banding in children with end stage LV dilated cardiomyopathy [54, 55]. Pulmonary artery banding was applied in 17 infants with dilated cardiomyopathy as compassionate care and was tolerated well. All of these 17 infants could be removed from transplant listing following marked improvements in LV size, function and clinical status [55]. In 12 infants, the pulmonary artery banding was subsequently released by trans-catheter technique with ten continuing to do well. This suggests that either the DCM was reversible, or that therapy through ventricular–ventricular interactions brought about sustained LV reverse remodeling. These 'proof-of-principle' results certainly require validation in larger prospective controlled trials but suggest that utilization of ventricular–ventricular interactions through pulmonary artery banding in LV failure may provide a novel, safe and effective therapeutic alternative; in this high-risk population.

Do Ventricular–Ventricular Interactions Affect Ventricular Function in Single-Ventricle Physiology?

While it is intuitive to discuss ventricular–ventricular interactions when there are two functioning ventricles, ventricular cross-talk may be just as important to ventricular mechanics when there is only one functioning ventricle, as occurs when either the RV or LV is severely under-developed. Using magnetic resonance imaging, Fogel demonstrated in children with a functionally single ventricle that regional myocardial strain, twist, and radial motion are markedly different to that seen in biventricular hearts [56]. In hypoplastic left heart syndrome for example, the absence of a developed LV may alter TV annular configuration and worsen TR, an important risk factor for adverse outcomes in this high-risk population [57]. Using strain imaging, we recently found that asymmetry in septal to lateral contraction at the tricuspid annulus in HLHS is associated with more TR [58]. This asymmetry manifested both in the degree of developed strain at the septal and lateral basal segments, and in the time to peak strain [58]. Likewise, a larger interventricular septum, as a marker of the dysfunctional/hypoplastic LV size, may be a risk factor for death or transplant in this population [59]. This may be yet another manifestation of the effects of ventricular–ventricular interactions on RV function. However, not all authors have found an effect of the size of the hypoplastic LV on RV function or outcomes in HLHS [60]. Thus, wall motion abnormalities, arising at least in part from adverse VVI, may contribute to adverse tricuspid valve geometry and function [61] in addition to the tricuspid valve structural abnormalities that underlie TR in HLHS [62].

Summary

In summary, ventricular–ventricular interactions profoundly affect right and left ventricular function in both normal conditions and in various disease states (Table 6.2), especially those characterized by increased afterload or preload. A better understanding of the pathophysiology of ventricular–ventricular interactions can lead to new therapeutic interventions that target or harness these interactions.

Table 6.2 Examples of conditions where ventricular–ventricular interactions have been shown to be important

Condition	Comment
Right-to-left interactions	
Increased RV afterload	
Pulmonary hypertension	Leftward septal shift, decreased LV preload, LV myocardial injury
RV outflow tract obstruction	Pulmonary stenosis and conduit obstruction after repair of Tetralogy of Fallot
Right ventricular infarction	Acute experimental models of right coronary artery ligation ligation
Increased RV preload	
Repaired Tetralogy of Fallot	RV dilatation leads to LV dysfunction
Left-to-right interactions	
Hypoplastic left heart syndrome	LV geometry and septal dysfunction may affect RV function. LV sinusoids in some patients may affect RV function
Aortic stenosis	Some patients have decreased RV function which improves after aortic balloon valvuloplasty

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