



Mechanical and Functional Interdependence Between the RV and LV

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Introduction

Although the left (LV) and right (RV) ventricles have different embryological origins, they are bound together through epicardial myofibers that encircle them, through myofibers that form a common apex, through the interventricular septum, their attachment to each other at the septal hinge points, the common pericardial space, the in-series configuration of the pulmonary and systemic circulation, and the coronary circulation [1, 2]. As a result, the RV and LV are anatomically and functionally connected. This tight coupling between the ventricles affects RV and LV function in health and disease. In normal physiology, RV and LV cardiac cycle events such as the onset of contraction, aortic and pulmonary flow, and RV and LV filling are closely aligned. In various conditions, such as adverse loading, electromechanical dyssynchrony, and ventricular failure, the alignment of these events is disrupted, further contributing to dysfunction and adverse ventricular-ventricular interactions. The impact of events and function in one ventricle on the contralateral ventricle is clinically important as in various diseases, RV and LV systolic functions

are linearly related [3, 4]. Moreover, coexisting LV dysfunction is a key risk factor for functional decline and mortality in diseases characterized by RV dysfunction [5], and concomitant RV failure is a risk factor for death in diseases primarily characterized by LV failure [6, 7].

Physiology of RV-LV Interactions

Over the past decades, fundamental experimental work has been instrumental in delineating the importance of ventricular-ventricular interactions to cardiac function and its mechanisms (Fig. 4.1). These experiments first delineated the contribution of the LV to normal RV function. In open-chest experiments, the RV was completely electrically separated from the LV by a full-thickness RV ventriculotomy, but then sewed together to restore mechanical continuity [8]. Thus, electrical stimulation of each ventricle individually, without activation of the entire heart, could delineate the hemodynamic effects of one ventricle on developed pressure in the ipsilateral and contralateral ventricle [8]. In this experiment, stimulating the LV led to almost normal RV pressure development and pulmonary blood flow. In fact, two waveforms for RV pressure and pulmonary arterial blood flow delineated the direct contribution of RV free-wall contraction, versus LV and septal contraction, to RV developed pressure. For RV pressure and pulmonary arterial blood flow, the LV and septal

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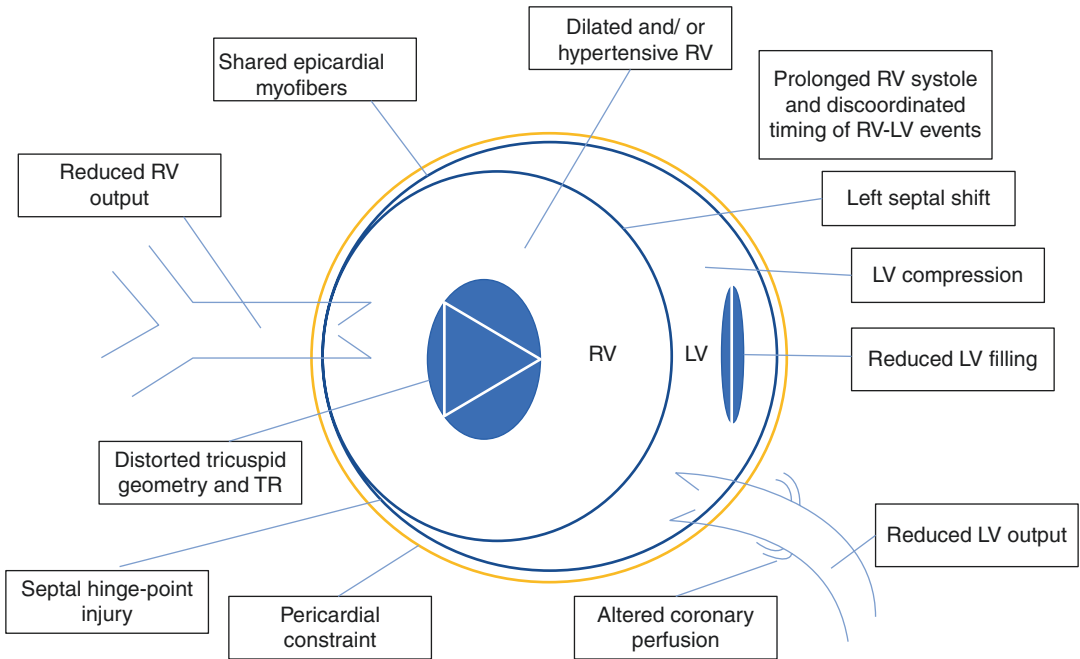


Fig. 4.1 Schematic representation of key mechanisms underlying adverse right ventricular (RV)-left ventricular (LV) interactions. Schematically depicted is a dilated RV with leftward septal shift, typical of severe pulmonary hypertension. These mechanisms manifest in other conditions as well as are detailed in the text. Within the constraints of the relatively fixed pericardial space, the hypertensive dilated RV compresses the LV and impedes its filling. Prolonged RV systolic duration and incoordinate timing of events contribute to this interaction and may impact RV and LV coronary filling and ischemia, thereby worsening dysfunction. RV dilatation predisposes to tricuspid regurgitation, which may further impede

effective RV output. Decreased RV output further reduces LV filling and LV output, with a resultant decrease in cardiac output. The distorted RV and LV geometry and septal shift increase wall stress in the septum and septal hinge-point regions which triggers molecular fibrosis signaling and fibrosis. These further worsen the function of the ischemic, metabolically challenged RV. Distorted septal and ventricular geometry further impairs the function of common myofibers in the septum and superficial epicardial layers contributing to RV and LV dysfunction. Several of these mechanisms can be targeted or leveraged therapeutically to improve contralateral ventricular function

contribution were larger than the RV free-wall component. In contrast, stimulating the RV to contract led to normal RV developed pressure, but minimal developed pressure in the LV [8]. Taking these experiments further by surgically disrupting the LV free wall, to prevent it from generating any force, further confirmed these observations, with a dramatic decrease of around 45% in the systolic pressure generated by the RV [9]. The differential influence of RV and LV contraction to RV developed pressure and output has also been shown in human subjects using pre-excitation of the RV by pacing or measuring hemodynamics during extrasystolic beats [10]. As in the experimental models, measurement of LV pressures during these events revealed the signifi-

cant contribution of LV contraction to pressure development in the human RV [10].

Consequently, modulating LV contractile force, for example by changing LV volume, or by occlusion of the left coronary artery, impedes RV developed pressure [9]. Indeed, these studies showed that over 50% of the mechanical work of the normal RV may be generated by LV contraction and that the LV free wall plays a pivotal role in RV function [9]. Moreover, even when the RV free wall is entirely replaced with a noncontractile prosthesis, so that there is a total lack of RV free-wall contraction, there is still near-normal RV pressure generation, as a consequence of normal LV shortening [11]. In some experiments, the change in RV developed force in response to

modulation of LV contraction, or loading, correlated with the degree of septal bulging into the RV cavity during systole, suggesting that the septum plays an important role in mediating these physiologic ventricular-ventricular interactions. Interestingly, however, surgically disrupting the septum did not affect RV developed pressure, but was associated with a dramatic decrease in LV developed pressure [12]. In contrast, injecting glutaraldehyde to the septum affected developed pressure in both ventricles [12]. The timing of contraction of the RV and LV further contributes to these interactions with LV contribution to RV developed pressure and pulmonary artery blood flow starting in the LV isovolumic contraction period [13].

These experiments show that under normal physiological conditions, the LV has enormous impact on RV pressure development and pulmonary arterial blood flow. This raises the question of what is the impact of the RV on normal LV function. The experiments above show that, under normal circumstances, RV contraction has little impact on developed pressure in the LV or on aortic blood flow. Even experimental ischemia of the RV free wall has minimal impact on LV developed pressure [12], and replacing the RV free wall with a noncontractile prosthesis had little effect on LV developed pressure and flow [11]. This may lead one to think that the RV has little effect on LV function, but this assumption would not be true. Firstly, the in-series configuration of the RV and LV determines that the flow generated by the RV through the pulmonary bed forms the LV preload. Additionally, changes in RV volume can profoundly affect LV contractile function. Indeed, in the aforementioned experiments that replaced the RV free wall with a noncontractile prosthesis, progressive enlargement of the noncontractile RV, by progressively repositioning a clamp along the prosthesis to increase RV cavity volume, led to progressive reduction in LV pressure development and stroke work [11]. In fact, changes in RV volume are associated with changes in the LV pressure-volume relation, which is a fundamental property and descriptor of ventricular function [10]. For example, experimental coronary artery ligation to induce acute

RV ischemia causes acute RV dilatation and reduced LV end-systolic elastance, a pressure-volume measure of contractility [14]. The change in LV function and output cannot be attributed solely to reduced LV volume secondary to RV dilatation as end-systolic elastance is a load-independent measure of LV contractility [14]. Interestingly, decreased LV end-systolic elastance secondary to RV ischemia could be reversed by creation of a superior vena cava to pulmonary artery shunt which “bypasses” the RV and reduces RV volume loading to restore more normal LV geometry [14]. This experimental observation has clinical implications in the treatment of complex congenital heart disease where placement of a superior vena cava to pulmonary artery shunt is commonly performed. The clinically important impact of RV volumes on LV stroke volume is also clinically evident during mechanical ventilation [15].

Compression of the LV during RV dilatation is dependent on the confined pericardial space that the ventricles share. In this situation, dilation of one ventricle in a confined space causes compression of the contralateral ventricle. Consequently, releasing the pericardium can normalize LV contractility even when the ischemic RV remains dilated [16]. In essence, this overlaps with the pathophysiology of cardiac tamponade where respiratory-dependent changes in RV and LV filling cause enlargement of one chamber, at the expense of the other, when the pericardial restraint or pressures are high.

RV-LV Interactions When the RV Is Hypertensive

The impact of a dilated RV on LV function becomes critical when the RV is additionally hypertensive. In patients with severe pulmonary arterial hypertension (PAH), RV dilatation compresses the LV within the confines of the relatively fixed, noncompliant, pericardial space, while high RV pressures displace the interventricular septum leftward [17]. The compressed LV and small LV volumes are further exacerbated by reduced preload due to RV dysfunction

and the resulting decreased stroke volume is ejected into the pulmonary bed [17]. The combination of these factors leads to reduced LV filling while the distorted LV geometry may impede its normal contractility [18–23]. The importance of these LV geometrical changes is demonstrated by the finding that in PAH, LV, more than RV, end-diastolic volume is linearly related to cardiac output [19]. The importance of the interaction between the dilated hypertensive RV and compressed LV is further confirmed by the LV eccentricity index being linked to catheter-measured hemodynamics as well as death or lung transplantation in children with PAH [24–27]. Although perhaps most emphasized in PAH, this pathophysiological mechanism is relevant to any condition with severe RV hypertension. For example, in patients with repaired tetralogy of Fallot with severe RV hypertension from RV-pulmonary artery conduit stenosis, prolonged septal shift and prolonged RV contraction produce reduced LV filling as the septum bulges into the LV during LV diastole [28]. Consequently, alleviating stenosis of the RV-PA conduit reduces RV hypertension and normalizes septal curvature and RV contraction time, which synchronizes LV and RV contraction and relaxation [28]. The restoration of normal RV-LV interactions increases LV diastolic filling and improves exercise capacity, which is an important clinical outcome in this population [28]. Impaired LV systolic function during RV hypertension induced by pulmonary artery constriction can partly be attributed to changed LV geometry and alterations at the septal insertion points where the RV and LV connect [23]. These alterations at the septal hinge points will be further detailed later in the chapter.

As these observations suggest, the temporal disparity between RV and LV cardiac cycle events compounds the geometrical interactions induced by left septal shift. In the hypertensive RV, be it from severe conduit stenosis or PAH, RV contraction and systolic time prolong because of prolonged isovolumic contraction and relaxation [29]. Prolongation of RV systole in the dysfunctional hypertensive RV causes peak RV myocardial shortening and persistence

of elevated RV pressures into early LV diastole, at the same time that LV pressures are rapidly falling during isovolumic relaxation and rapid filling [20, 30]. This causes an abrupt leftward shift of the interventricular septum exactly as the LV is rapidly relaxing and the mitral valve is opening, impeding the dominant phase of LV filling in early LV diastole [30]. Consequently children with PAH exhibit impaired LV diastolic filling and function [26]. These adverse geometrical-temporal RV-LV interactions worsen with increasing heart rate, as diastole, and the time available for ventricular filling, is disproportionately shortened versus systole by heart rate [29]. The systolic to diastolic duration ratio, as measured from the duration of tricuspid regurgitation spectral Doppler [29], or strain imaging [20, 31], is a marker of RV systolic prolongation and decreased RV and LV filling, associated with death or lung transplantation [29]. The result of shortened RV diastolic duration and impaired LV filling is clinically important reduced stroke volume and cardiac output [19, 32–34]. The compromised hemodynamics are further worsened by inefficient RV pump function, as even though RV contraction (systolic duration) is prolonged, the short RV ejection time due to the high pulmonary vascular resistance compromises RV output, LV preload, and consequently LV filling and cardiac output [34]. These adverse interactions translate into clinical outcomes as left septal shift, LV filling, and RV systolic to diastolic duration ratio are linked to clinical outcome [29, 35].

As mentioned above, RV hypertension, dilation, and septal displacement further compromise efficient RV pump function and RV-LV interactions as they lead to incoordinate RV contraction between the septum and lateral wall and between the RV and LV lateral walls [34, 36–39]. An interventricular mechanical delay, that can occur in both RV and LV dysfunction, may further worsen LV function as well as increase the risk of arrhythmia and decrease exercise tolerance [40, 41]. The pathophysiological effect of incoordinate RV and LV cardiac cycle events also becomes evident during support of the LV by an assist device. LV assist devices are associated

with shortening of LV systolic duration, disparity between LV and RV filling, and reduction in LV stroke volume secondary to reduced preload [42]. These experimental findings translate into clinical decision-making, as the speed setting in the LV assist device impacts LV sphericity, rightward septal bulge, LV-RV interactions, and RV filling, all of which ultimately affect cardiac output [43]. While the above observations emphasize RV systolic interactions, diastolic RV-LV interactions are also important. During lower body suction in patients with heart failure, decreased RV end-diastolic volume results in increased LV end-diastolic volume despite reduced pulmonary capillary wedge pressure [44, 45]. Experimentally, RV free-wall stiffening, which occurs when the RV is hypertensive [46], leads to increased septal diastolic length and increased LV stiffness, even when LV volume is constant [47]. This interaction may be mediated by the common myocardial tracts encircling the two ventricles.

Mediation of ventricular-ventricular interactions through the common myocardial tracts is also invoked as LV geometrical-temporal interactions do not account for all the adverse RV-LV interactions described above. When the RV acutely dilates secondary to right coronary obstruction and ischemia within the pericardium, there is a compression of the LV, but also impaired LV contractility that is independent of loading conditions [16]. Although leftward septal displacement within the constraints of the noncompliant pericardium is crucial in mediating ventricular interactions [48], release of the pericardium leads to restoration of LV contractility that is not solely attributable to reduced LV volume or distorted LV geometry [16]. These load-independent changes in LV contractility may stem from changed contractility in the shared superficial myofiber tracts running between the ventricles [18, 49, 50].

These shared myocardial tracts can be leveraged for therapeutic benefit. It had previously been established that acutely constricting the aorta during acute increases in RV afterload leads to increased stroke volume [51]. Although changed coronary flow patterns may explain beneficial effects of supra-aortic banding in RV pres-

sure loading, these experiments kept coronary flow constant, so that the effects occurred independent of right coronary artery perfusion [51]. This demonstrates that, under these circumstances, there are additional factors that contribute to RV-LV interactions, most likely the shared epicardial and septal fibers [52, 53].

Increasing of the contralateral ventricle's afterload to improve ipsilateral ventricular function is also used in patients who have congenitally corrected transposition of the great arteries and tricuspid regurgitation. In this congenital heart disease, the RV is the systemic ventricle and the tricuspid valve is often malformed ("Ebstein-like") and regurgitant [54]. Often, the dilated, systemic RV and interventricular septum bulge towards the LV, further distorting the tricuspid annulus with progressively worsening tricuspid regurgitation and RV dilation [55]. Pulmonary artery banding can be used in these patients to increase LV afterload and pressure, so that the septum shifts towards the RV, into a more neutral position, thereby improving TV annular configuration and reducing TR [55]. In this condition, pulmonary artery banding may also increase contractility of the sub-pulmonary LV, leading to increased contractility of the systemic RV through the shared myocardial fibers. However, in practice, placing an adequately tight band to induce LV pressure load on the one hand, while avoiding LV failure from excessive pressure loading on the other, is a delicate balance and one not easily assessed. Increasing the contralateral ventricle's afterload has also been harnessed in children with severe dilated LV cardiomyopathy and left-heart failure, where pulmonary artery banding in carefully selected patients can lead to reduced LV dilatation, decreased mitral regurgitation, and increased LVEF [56].

The systolic interactions between the RV and LV are mediated not only by changes in septal position, and the common superficial myocardial tracts, but also by the oblique orientation of the myofibers in the interventricular septum [57]. In left-heart failure, as the LV remodels and progressively becomes more spherical, the septal fibers lose their oblique angle, thereby reducing

their mechanical efficiency to reduce not only LV, but also RV contractile function. The decrease in RV function can lead to increasing tricuspid regurgitation and further RV dilatation, and a vicious cycle of additional reduction in the oblique angle of the septal myofibers [57].

Mechanical-Molecular RV-LV Interactions in RV Hypertension

Our group's experiments in a more chronic rabbit model of RV hypertension from pulmonary artery banding further extended the potential therapeutic effects of harnessing common myocardial fibers discussed above in regard to the benefits of acute aortic constriction on RV function during acute RV hypertension [52]. We found that RV hypertension leads to RV and LV dysfunction and impaired contractile function in association with myocyte hypertrophy and development of interstitial fibrosis [52]. By adding a mildly constricting aortic band, we obtained an increase in RV contractility without compromising LV contractility (indeed there was even a small increase in LV contractility) [52]. This functional benefit was associated with improved histological findings including decreased extracellular matrix remodeling, decreased biventricular fibrosis, and decreased profibrotic molecular signaling through the transforming growth factor beta (TGF β 1) and endothelin (ET)-1 pathways [52, 58, 59]. Similarly, in juvenile rabbits with RV hypertension and pulmonary artery banding, septal apoptosis, fibrosis, and reduced capillary density develop and extend to the LV free wall [60]. The improved RV and LV function with addition of a mild aortic band in the pulmonary artery band rabbit model may also stem from partial reversal of leftward septal displacement, improved RV and LV geometry, and increased LV contractility secondary to the increased LV load. The development of RV and LV fibrosis secondary to RV hypertension can also be ameliorated by pharmacological therapy including angiotensin receptor and ET-1 receptor blockade which reduce TGF β 1 signaling [58, 59, 61].

RV-LV Interactions at the Septal Hinge-Point Regions

The geometrical-temporal RV-LV cross talk in RV hypertension occurs, at least in part, at the septal hinge-point regions where increased shear stress and regional injury occur [21, 62, 63]. Indeed, LV circumferential and RV longitudinal shortening at the RV septal insertion regions contribute to increased stress, shear forces, and fibrosis [21, 64, 65]. These increased mechanical stresses trigger mechanotransduction and molecular signaling through integrins to upregulate transforming growth factor beta (TGF β) signaling that ultimately is associated with extracellular matrix remodeling and fibrosis [66]. This mechanotransduction signaling is most prominent in the hypertensive RV and septal hinge-point regions [63, 66]. However, effects may not all be detrimental, as concomitantly with increased fibrosis, we also found increased elastin deposition at the septal hinge points [66]. Elastin, a more compliant material than stiff fibrillar collagen, may serve to increase compliance in these septal connecting regions, thereby partially buffering the LV from adverse myocardial RV-LV interactions [66].

The high-stress septal hinge-point areas also manifest clinically in human PAH patients, where MRI delayed gadolinium enhancement fibrosis imaging is increased at the RV septal insertion points in relation to the severity of RV afterload [64, 67, 68]. Thus, septal hinge-point fibrosis may be clinically important as it is associated with reduced RV function and increased mortality [64, 67]. In children with PAH, we found that decreased LV myocardial shortening was most prominent at the septum, consistent with the experimental and clinical findings at the septal hinge-point regions [69].

Similar to findings in rat and rabbit PAB models, mice with PAB demonstrate impaired RV and LV systolic function along with decreased LV stroke work, torsion and torsion rate, and mildly increased LV fibrosis, attributed to increased myocardial stress [70]. The LV histological and functional changes and fibrosis were accompanied by increased β -MHC expression and

decreased expression of Ca^{2+} -handling proteins [70]. The changes in α - and β -MHC expression were in turn associated with the changes in LV mechanics. Interestingly, the association between increased RV pressure loading and decreased LV torsion mechanics is in contrast to findings from acute experiments where the LV responded to an acute increase in RV pressure loading and decreased RV stroke volume by an acute increase in torsion and untwist rate [71]. The differences between these results may possibly be explained by the development of myocardial hypertrophy and fibrosis in the chronic models and by differences in volume loading, coronary perfusion, and different myocardial mechanics in acute versus chronic conditions. Indeed, acute RV pressure loading can lead to acute decreases in LV contractility, developed pressure, diastolic volume, and cardiac output that correlate with decreased LV and septal circumferential strain, LV untwisting, and apical rotation [72]. The septal circumferential strain, which likely correlates with septal oblique myofibers described above, was the most important factor associated with reduced LV performance [72].

Therapeutic Targeting of Molecular-Tissue RV-LV Interactions in RV Hypertension

Increasing the pressure load of the contralateral ventricle through aortic or pulmonary artery banding may be effective in changing ventricular geometry, septal position, and contralateral ventricular contractility. However, this invasive approach may be difficult to apply clinically in fragile patients. Consequently, pharmacologically inhibiting the adverse molecular signaling in the RV and the septal hinge-point regions leading to tissue injury and increased fibrosis may be a therapeutic option to address the molecular-tissue effects of adverse RV-LV interactions. As detailed above, in PAB rabbit models, we showed that angiotensin and endothelin-receptor blockades, both of which decrease $\text{TGF}\beta$ signaling, lead to decreased biventricular fibrosis and improved biventricular function [58, 59, 61].

Pharmacological therapy to reduce heart rate may also be beneficial in certain circumstances to address the temporal aspects of adverse RV-LV interactions in RV pressure loading and PAH. In rat models of PAH and pulmonary artery banding, we showed that slowing heart rate using the beta-adrenergic receptor antagonist carvedilol, or the non-adrenergic agent ivabradine, improves RV and LV function through alignment of RV and LV events [73–75]. We attributed this realignment in RV-LV events to improved RV diastolic relaxation, possibly due to improved Ca^{2+} cycling [73–75]. Importantly, the improved biventricular function was associated with reduced fibrosis and cardiomyocyte hypertrophy, even though RV systolic pressures and RV-LV geometry and compression were unchanged, showing that heart rate-reducing agents were not acting through alleviation of pulmonary arterial or RV pressures [73–75].

RV-LV Interactions in Congenital Heart Disease

Because of pressure and/or volume loading and distorted ventricular structure and geometry, various congenital heart diseases can demonstrate the physiological and clinical importance of ventricular-ventricular interactions. An intriguing example is when one of the ventricles is severely hypoplastic. Functionally single ventricles have markedly altered myocardial mechanics including myocardial shortening, twist, and radial motion. While these may be impacted by multiple factors, the lack of a contralateral ventricle may constitute one of these factors. An example of such adverse interactions can be seen in hypoplastic left-heart syndrome, where the direct and indirect impacts of an underdeveloped LV may alter RV and TV annular configuration and worsen TR, which increases the risk for death or need for heart transplant [76]. The presence of a small LV can also distort RV geometry and cause RV apical bulging, which we found to be associated with impaired RV mechanics and increased risk for heart transplant or death [77]. We further found diminished septal strain in

HLHS patients with a moderately hypoplastic LV (and hence relatively larger LV) versus a diminutive (and hence almost absent) LV, in association with asymmetric RV mechanics and worse clinical outcome [78]. Thus, the presence of a hypoplastic LV may be worse than having no discernable LV, as RV geometry appears to be adversely affected.

A maldeveloped RV can also impact LV function, as occurs in Ebstein's anomaly of the tricuspid valve. In this condition, the tricuspid septal and inferior leaflets are displaced and rotated apically and towards the RV outflow tract. This yields a variable length of the interventricular septum as part of functional right atrium, a small "functional" RV distal to the displaced tricuspid leaflets, that has impaired myocardial function, and variable but often severe TR. In these children, we found that an early diastolic leftward interventricular shift is found in most patients and associated with decreased LV filling and with more TR [79]. Moreover, reduced pulmonary artery antegrade flow was associated with lower LV filling, LV volumes, LVEF, and output. Importantly, from a clinical perspective, impaired LV systolic and diastolic volumes and performance were associated with reduced exercise capacity [79]. We hypothesized that prolonged RV systole and increased TR may impede LV filling, whereas decreased LVEF, SV, systolic strain, and delayed aortic and atrioventricular valve opening and closure suggest impaired contractile force development, possibly related to enlargement and dysfunction of the "functional" RV (the portion of the RV that remains distal to the displaced tricuspid valve). We also hypothesized that early rightward IVS motion may impede LV systolic function, and an ineffective leftward systolic septal shift may impede pressure development [79]. Thus, although the pathophysiology is completely different from PAH, some of the adverse RV-LV interactions have similar features stemming from impaired RV contractile function and disparate RV and LV events and geometry. Indeed, severe Ebstein's anomaly that manifests clinically in the early neonatal period can be very difficult to manage,

even if the LV functions well. Thus, the RV is clearly central to cardiac function and clinical outcomes in these situations.

The effects of an abnormal RV on the LV are also apparent in repaired tetralogy of Fallot. Tetralogy of Fallot is a cyanotic congenital heart disease characterized by RV outflow tract obstruction and a large ventricular septal defect. After surgical "repair" in infancy, which patch-closes the ventricular septal defect and relieves RV outflow tract obstruction, there is often pulmonary regurgitation due to disruption of the pulmonary valve [80]. Consequently, chronic RV volume loading and dilatation impact both RV and LV filling, function, and mechanics [81]. RV dilatation is associated with impaired LV intracavitary flow patterns, specifically, LV diastolic flow and flow of the residual blood volume that is retained in the ventricle after ejection [82]. These impaired LV flow patterns correlate with reduced LV circumferential shortening and ejection fraction [82]. These abnormal flow patterns are likely associated with impaired LV kinetic energy [83]. Reduced LV twist and strain have also been found in this population, in relation to RV dilatation [4, 84–88]. The common apical myofibers, which determine to a large extent LV twist-untwist, may be responsible for the decrease in LV torsion, and consequently decreases in LV intraventricular pressure gradients and diastolic suction [89, 90]. Indeed, even though tetralogy of Fallot is thought to be a "right-heart" disease, both RV and LV diastolic functions are impaired after tetralogy of Fallot surgical repair, in part due to the effects of adverse ventricular-ventricular interactions [91–93]. The association between RV and LV function in repaired tetralogy of Fallot is also found at the myocardial level [94]. Our group showed that reduced LV early diastolic deformation is associated with RV dilatation and pulmonary regurgitation [91]. However, LV dysfunction in repaired tetralogy of Fallot may not only stem from RV abnormalities. Aortic dilatation is very common after tetralogy of Fallot repair and may be associated with increased aortic shear stress, stiffness, and abnormal flow that may directly impact LV function [95, 96].

Summary

In summary, the RV and LV are tightly linked. Consequently, function and events in one ventricle can profoundly impact the contralateral ventricle. These adverse interactions are found in diverse acquired and congenital heart diseases and seem to be critical in severe RV hypertension, most importantly PAH. The challenge is often to determine which outcomes are due to adverse RV-LV interactions versus ipsilateral effects. Answering this question will assist in designing therapies that can leverage beneficial ventricular-ventricular interactions while reducing the effects of adverse RV-LV interactions.

References

- Appleyard RF, Glantz SA. Pulmonary model to predict the effects of series ventricular interaction. *Circ Res.* 1990;67(5):1225–37.
- Slinker BK, Glantz SA. End-systolic and end-diastolic ventricular interaction. *Am J Physiol.* 1986;251(5 Pt 2):H1062–75.
- Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, et al. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. *J Am Coll Cardiol.* 2002;40(11):2044–52.
- Kempny A, Diller GP, Orwat S, Kaleschke G, Kerckhoff G, Bunck A, et al. Right ventricular-left ventricular interaction in adults with tetralogy of Fallot: a combined cardiac magnetic resonance and echocardiographic speckle tracking study. *Int J Cardiol.* 2012;154(3):259–64.
- Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol.* 2002;40(9):1675–80.
- Gulati A, Ismail TF, Jabbour A, Alpendurada F, Guha K, Ismail NA, et al. The prevalence and prognostic significance of right ventricular systolic dysfunction in nonischemic dilated cardiomyopathy. *Circulation.* 2013;128(15):1623–33.
- Alhamshari YS, Alnabelsi T, Mulki R, Cepeda-Valery B, Figueredo VM, Romero-Corral A. Right ventricular function measured by TAPSE in obese subjects at the time of acute myocardial infarction and 2 year outcomes. *Int J Cardiol.* 2017;232:181–5.
- Damiano RJ Jr, La Follette P Jr, Cox JL, Lowe JE, Santamore WP. Significant left ventricular contribution to right ventricular systolic function. *Am J Physiol.* 1991;261(5 Pt 2):H1514–24.
- Santamore WP, Lynch PR, Heckman JL, Bove AA, Meier GD. Left ventricular effects on right ventricular developed pressure. *J Appl Physiol.* 1976;41(6):925–30.
- Feneley MP, Gavaghan TP, Baron DW, Branson JA, Roy PR, Morgan JJ. Contribution of left ventricular contraction to the generation of right ventricular systolic pressure in the human heart. *Circulation.* 1985;71(3):473–80.
- Hoffman D, Sisto D, Frater RW, Nikolic SD. Left-to-right ventricular interaction with a noncontracting right ventricle. *J Thorac Cardiovasc Surg.* 1994;107(6):1496–502.
- Li KS, Santamore WP. Contribution of each wall to biventricular function. *Cardiovasc Res.* 1993;27(5):792–800.
- Schertz C, Pinsky MR. Effect of the pericardium on systolic ventricular interdependence in the dog. *J Crit Care.* 1993;8(1):17–23.
- Danton MH, Byrne JG, Flores KQ, Hsin M, Martin JS, Laurence RG, et al. Modified Glenn connection for acutely ischemic right ventricular failure reverses secondary left ventricular dysfunction. *J Thorac Cardiovasc Surg.* 2001;122(1):80–91.
- Mitchell JR, Whitelaw WA, Sas R, Smith ER, Tyberg JV, Belenkie I. RV filling modulates LV function by direct ventricular interaction during mechanical ventilation. *Am J Physiol Heart Circ Physiol.* 2005;289(2):H549–57.
- Brookes C, Ravn H, White P, Moeldrup U, Oldershaw P, Redington A. Acute right ventricular dilatation in response to ischemia significantly impairs left ventricular systolic performance. *Circulation.* 1999;100(7):761–7.
- Friedberg MK. Imaging right-left ventricular interactions. *JACC Cardiovasc Imaging.* 2018;11(5):755–71.
- Moulopoulos SD, Sarcas A, Stamatelopoulos S, Arealis E. Left ventricular performance during bypass or distension of the right ventricle. *Circ Res.* 1965;17(6):484–91.
- Gan C, Lankhaar JW, Marcus JT, Westerhof N, Marques KM, Bronzwaer JG, et al. Impaired left ventricular filling due to right-to-left ventricular interaction in patients with pulmonary arterial hypertension. *Am J Physiol Heart Circ Physiol.* 2006;290(4):H1528–33.
- Marcus JT, Vonk Noordegraaf A, Roelvelde RJ, Postmus PE, Heethaar RM, Van Rossum AC, et al. Impaired left ventricular filling due to right ventricular pressure overload in primary pulmonary hypertension: noninvasive monitoring using MRI. *Chest.* 2001;119(6):1761–5.
- Nelson GS, Sayed-Ahmed EY, Kroeker CA, Sun YH, Keurs HE, Shrive NG, et al. Compression of interventricular septum during right ventricular

- pressure loading. *Am J Physiol Heart Circ Physiol.* 2001;280(6):H2639–48.
22. Roelvelde RJ, Marcus JT, Faes TJ, Gan TJ, Boonstra A, Postmus PE, et al. Interventricular septal configuration at MR imaging and pulmonary arterial pressure in pulmonary hypertension. *Radiology.* 2005;234(3):710–7.
 23. Visner MC, Arentzen CE, O'Connor MJ, Larson EV, Anderson RW. Alterations in left ventricular three-dimensional dynamic geometry and systolic function during acute right ventricular hypertension in the conscious dog. *Circulation.* 1983;67(2):353–65.
 24. Burkett DA, Patel SS, Mertens L, Friedberg MK, Ivy DD. Relationship between left ventricular geometry and invasive hemodynamics in pediatric pulmonary hypertension. *Circ Cardiovasc Imaging.* 2020;13(5):e009825.
 25. Kassem E, Humpl T, Friedberg MK. Prognostic significance of 2-dimensional, M-mode, and Doppler echo indices of right ventricular function in children with pulmonary arterial hypertension. *Am Heart J.* 2013;165(6):1024–31.
 26. Burkett DA, Slorach C, Patel SS, Redington AN, Ivy DD, Mertens L, et al. Impact of pulmonary hemodynamics and ventricular interdependence on left ventricular diastolic function in children with pulmonary hypertension. *Circ Cardiovasc Imaging.* 2016;9(9):e004612.
 27. Jone PN, Hinzman J, Wagner BD, Ivy DD, Younoszai A. Right ventricular to left ventricular diameter ratio at end-systole in evaluating outcomes in children with pulmonary hypertension. *J Am Soc Echocardiogr.* 2014;27(2):172–8.
 28. Lurz P, Puranik R, Nordmeyer J, Muthurangu V, Hansen MS, Schievano S, et al. Improvement in left ventricular filling properties after relief of right ventricle to pulmonary artery conduit obstruction: contribution of septal motion and interventricular mechanical delay. *Eur Heart J.* 2009;30(18):2266–74.
 29. Alkon J, Humpl T, Manlihot C, McCrindle BW, Reyes JT, Friedberg MK. Usefulness of the right ventricular systolic to diastolic duration ratio to predict functional capacity and survival in children with pulmonary arterial hypertension. *Am J Cardiol.* 2010;106(3):430–6.
 30. Driessen MM, Hui W, Bijns BH, Dragulescu A, Mertens L, Meijboom FJ, et al. Adverse ventricular-ventricular interactions in right ventricular pressure load: insights from pediatric pulmonary hypertension versus pulmonary stenosis. *Physiol Rep.* 2016;4(11):e12833.
 31. Hui W, Slorach C, Iori S, Dragulescu A, Mertens L, Friedberg MK. The right ventricular myocardial systolic-to-diastolic duration ratio in children after surgical repair of tetralogy of Fallot. *J Appl Physiol* (1985). 2020;128(6):1677–83.
 32. Taylor RR, Covell JW, Sonnenblick EH, Ross J Jr. Dependence of ventricular distensibility on filling of the opposite ventricle. *Am J Physiol.* 1967;213(3):711–8.
 33. Duffels MG, Hardzilyenka M, Surie S, de Bruin-Bon RH, Hoendermis ES, van Dijk AP, et al. Duration of right ventricular contraction predicts the efficacy of bosentan treatment in patients with pulmonary hypertension. *Eur J Echocardiogr.* 2009;10(3):433–8.
 34. Gurudevan SV, Malouf PJ, Auger WR, Waltman TJ, Madani M, Raisinghani AB, et al. Abnormal left ventricular diastolic filling in chronic thromboembolic pulmonary hypertension: true diastolic dysfunction or left ventricular underfilling? *J Am Coll Cardiol.* 2007;49(12):1334–9.
 35. Mahmud E, Raisinghani A, Hassankhani A, Sadeghi HM, Strachan GM, Auger W, et al. Correlation of left ventricular diastolic filling characteristics with right ventricular overload and pulmonary artery pressure in chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol.* 2002;40(2):318–24.
 36. Kalogeropoulos AP, Georgiopoulou VV, Howell S, Pernetz MA, Fisher MR, Lerakis S, et al. Evaluation of right intraventricular dyssynchrony by two-dimensional strain echocardiography in patients with pulmonary arterial hypertension. *J Am Soc Echocardiogr.* 2008;21(9):1028–34.
 37. Lopez-Candales A, Dohi K, Rajagopalan N, Suffoletto M, Murali S, Gorcsan J, et al. Right ventricular dyssynchrony in patients with pulmonary hypertension is associated with disease severity and functional class. *Cardiovasc Ultrasound.* 2005;3:23.
 38. Vonk-Noordegraaf A, Marcus JT, Gan CT, Boonstra A, Postmus PE. Interventricular mechanical asynchrony due to right ventricular pressure overload in pulmonary hypertension plays an important role in impaired left ventricular filling. *Chest.* 2005;128(6 Suppl):628S–30S.
 39. Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Gotte MJ, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. *J Am Coll Cardiol.* 2008;51(7):750–7.
 40. D'Andrea A, Caso P, Sarubbi B, D'Alto M, Giovanna Russo M, Scherillo M, et al. Right ventricular myocardial activation delay in adult patients with right bundle branch block late after repair of tetralogy of Fallot. *Eur J Echocardiogr.* 2004;5(2):123–31.
 41. Hui W, Slorach C, Friedberg MK. Apical transverse motion is associated with interventricular mechanical delay and decreased left ventricular function in children with dilated cardiomyopathy. *J Am Soc Echocardiogr.* 2018;31(8):943–50.
 42. Shimamura J, Nishimura T, Mizuno T, Takewa Y, Tsukiya T, Inatomi A, et al. Quantification of interventricular dyssynchrony during continuous-flow left ventricular assist device support. *J Artif Organs.* 2019;22(4):269–75.
 43. Addetia K, Uriel N, Maffessanti F, Sayer G, Adatya S, Kim GH, et al. 3D morphological changes in LV and RV during LVAD ramp studies. *JACC Cardiovasc Imaging.* 2018;11(2 Pt 1):159–69.

44. Tyberg JV, Belenkie I, Manyari DE, Smith ER. Ventricular interaction and venous capacitance modulate left ventricular preload. *Can J Cardiol*. 1996;12(10):1058–64.
45. Atherton JJ, Moore TD, Lele SS, Thomson HL, Galbraith AJ, Belenkie I, et al. Diastolic ventricular interaction in chronic heart failure. *Lancet*. 1997;349(9067):1720–4.
46. Rain S, Andersen S, Najafi A, Gammelgaard Schultz J, da Silva Goncalves Bos D, Handoko ML, et al. Right ventricular myocardial stiffness in experimental pulmonary arterial hypertension: relative contribution of fibrosis and myofibril stiffness. *Circ Heart Fail*. 2016;9(7):e002636.
47. Shirakabe M, Yamaguchi S, Tamada Y, Baniya G, Fukui A, Miyawaki H, et al. Impaired distensibility of the left ventricle after stiffening of the right ventricle. *J Appl Physiol* (1985). 2001;91(1):435–40.
48. Kroeker CA, Shrive NG, Belenkie I, Tyberg JV. Pericardium modulates left and right ventricular stroke volumes to compensate for sudden changes in atrial volume. *Am J Physiol Heart Circ Physiol*. 2003;284(6):H2247–54.
49. Sanchez-Quintana D, Climent V, Ho SY, Anderson RH. Myoarchitecture and connective tissue in hearts with tricuspid atresia. *Heart*. 1999;81(2):182–91.
50. Smerup M, Nielsen E, Agger P, Frandsen J, Vestergaard-Poulsen P, Andersen J, et al. The three-dimensional arrangement of the myocytes aggregated together within the mammalian ventricular myocardium. *Anat Rec (Hoboken)*. 2009;292(1):1–11.
51. Belenkie I, Horne SG, Dani R, Smith ER, Tyberg JV. Effects of aortic constriction during experimental acute right ventricular pressure loading. Further insights into diastolic and systolic ventricular interaction. *Circulation*. 1995;92(3):546–54.
52. Apitz C, Honjo O, Humpl T, Li J, Assad RS, Cho MY, et al. Biventricular structural and functional responses to aortic constriction in a rabbit model of chronic right ventricular pressure overload. *J Thorac Cardiovasc Surg*. 2012;144(6):1494–501.
53. Apitz C, Honjo O, Friedberg MK, Assad RS, Van Arsdell G, Humpl T, et al. Beneficial effects of vasopressors on right ventricular function in experimental acute right ventricular failure in a rabbit model. *Thorac Cardiovasc Surg*. 2012;60(1):17–23.
54. Prieto LR, Hordof AJ, Secic M, Rosenbaum MS, Gersony WM. Progressive tricuspid valve disease in patients with congenitally corrected transposition of the great arteries. *Circulation*. 1998;98(10):997–1005.
55. Kral Kollars CA, Gelehrter S, Bove EL, Ensing G. Effects of morphologic left ventricular pressure on right ventricular geometry and tricuspid valve regurgitation in patients with congenitally corrected transposition of the great arteries. *Am J Cardiol*. 2010;105(5):735–9.
56. Schranz D, Rupp S, Muller M, Schmidt D, Bauer A, Valeske K, et al. Pulmonary artery banding in infants and young children with left ventricular dilated cardiomyopathy: a novel therapeutic strategy before heart transplantation. *J Heart Lung Transplant*. 2013;32(5):475–81.
57. Schwarz K, Singh S, Dawson D, Frenneaux MP. Right ventricular function in left ventricular disease: pathophysiology and implications. *Heart Lung Circ*. 2013;22(7):507–11.
58. Ramos SR, Pielek G, Sun M, Slorach C, Hui W, Friedberg MK. Early versus late cardiac remodeling during right ventricular pressure load and impact of preventive versus rescue therapy with endothelin-1 receptor blockers. *J Appl Physiol* (1985). 2018;124(5):1349–62.
59. Nielsen EA, Sun M, Honjo O, Hjortdal VE, Redington AN, Friedberg MK. Dual endothelin receptor blockade abrogates right ventricular remodeling and biventricular fibrosis in isolated elevated right ventricular afterload. *PLoS One*. 2016;11(1):e0146767.
60. Kitahori K, He H, Kawata M, Cowan DB, Friehs I, Del Nido PJ, et al. Development of left ventricular diastolic dysfunction with preservation of ejection fraction during progression of infant right ventricular hypertrophy. *Circ Heart Fail*. 2009;2(6):599–607.
61. Friedberg MK, Cho MY, Li J, Assad RS, Sun M, Rohailla S, et al. Adverse biventricular remodeling in isolated right ventricular hypertension is mediated by increased transforming growth factor-beta1 signaling and is abrogated by angiotensin receptor blockade. *Am J Respir Cell Mol Biol*. 2013;49(6):1019–28.
62. Gold J, Akazawa Y, Sun M, Hunter KS, Friedberg MK. Relation between right ventricular wall stress, fibrosis, and function in right ventricular pressure loading. *Am J Physiol Heart Circ Physiol*. 2020;318(2):H366–H77.
63. Nielsen EA, Okumura K, Sun M, Hjortdal VE, Redington AN, Friedberg MK. Regional septal hinge-point injury contributes to adverse biventricular interactions in pulmonary hypertension. *Physiol Rep*. 2017;5(14):e13332.
64. McCann GP, Gan CT, Beek AM, Niessen HW, Vonk Noordegraaf A, van Rossum AC. Extent of MRI delayed enhancement of myocardial mass is related to right ventricular dysfunction in pulmonary artery hypertension. *AJR Am J Roentgenol*. 2007;188(2):349–55.
65. Beyar R, Dong SJ, Smith ER, Belenkie I, Tyberg JV. Ventricular interaction and septal deformation: a model compared with experimental data. *Am J Phys*. 1993;265(6 Pt 2):H2044–56.
66. Sun M, Ishii R, Okumura K, Krauszman A, Breitling S, Gomez O, et al. Experimental right ventricular hypertension induces regional beta1-integrin-mediated transduction of hypertrophic and profibrotic right and left ventricular signaling. *J Am Heart Assoc*. 2018;7(7):e007928.
67. Shehata ML, Lossnitzer D, Skrok J, Boyce D, Lechtzin N, Mathai SC, et al. Myocardial delayed enhancement

- in pulmonary hypertension: pulmonary hemodynamics, right ventricular function, and remodeling. *AJR Am J Roentgenol.* 2011;196(1):87–94.
68. Sanz J, Dellegrattaglia S, Kariisa M, Sulica R, Poon M, O'Donnell TP, et al. Prevalence and correlates of septal delayed contrast enhancement in patients with pulmonary hypertension. *Am J Cardiol.* 2007;100(4):731–5.
 69. Burkett DA, Slorach C, Patel SS, Redington AN, Ivy DD, Mertens L, et al. Left ventricular myocardial function in children with pulmonary hypertension: relation to right ventricular performance and hemodynamics. *Circ Cardiovasc Imaging.* 2015;8(8):e003260.
 70. Kheyfets VO, Dufva MJ, Boehm M, Tian X, Qin X, Tabakh JE, et al. The left ventricle undergoes biomechanical and gene expression changes in response to increased right ventricular pressure overload. *Physiol Rep.* 2020;8(9):e14347.
 71. Cho EJ, Jiamsripong P, Calleja AM, Alharthi MS, McMahon EM, Chandrasekaran K, et al. The left ventricle responds to acute graded elevation of right ventricular afterload by augmentation of twist magnitude and untwist rate. *J Am Soc Echocardiogr.* 2011;24(8):922–9.
 72. Chua J, Zhou W, Ho JK, Patel NA, Mackensen GB, Mahajan A. Acute right ventricular pressure overload compromises left ventricular function by altering septal strain and rotation. *J Appl Physiol* (1985). 2013;115(2):186–93.
 73. Gomez O, Okumura K, Honjo O, Sun M, Ishii R, Bijnsens B, et al. Heart rate reduction improves biventricular function and interactions in experimental pulmonary hypertension. *Am J Physiol Heart Circ Physiol.* 2018;314(3):H542–H51.
 74. Ishii R, Okumura K, Akazawa Y, Malhi M, Ebata R, Sun M, et al. Heart rate reduction improves right ventricular function and fibrosis in pulmonary hypertension. *Am J Respir Cell Mol Biol.* 2020;63(6):843–55.
 75. Okumura K, Kato H, Honjo O, Breitling S, Kuebler WM, Sun M, et al. Carvedilol improves biventricular fibrosis and function in experimental pulmonary hypertension. *J Mol Med (Berl).* 2015;93(6):663–74.
 76. Takahashi K, Inage A, Rebeyka IM, Ross DB, Thompson RB, Mackie AS, et al. Real-time 3-dimensional echocardiography provides new insight into mechanisms of tricuspid valve regurgitation in patients with hypoplastic left heart syndrome. *Circulation.* 2009;120(12):1091–8.
 77. Rosner A, Bharucha T, James A, Mertens L, Friedberg MK. Impact of right ventricular geometry and left ventricular hypertrophy on right ventricular mechanics and clinical outcomes in hypoplastic left heart syndrome. *J Am Soc Echocardiogr.* 2019;32(10):1350–8.
 78. Forsha D, Li L, Joseph N, Kutty S, Friedberg MK. Association of left ventricular size with regional right ventricular mechanics in hypoplastic left heart syndrome. *Int J Cardiol.* 2020;298:66–71.
 79. Fujioka T, Kuhn A, Sanchez-Martinez S, Bijnsens BH, Hui W, Slorach C, et al. Impact of interventricular interactions on left ventricular function, stroke volume, and exercise capacity in children and adults with Ebstein's anomaly. *JACC Cardiovasc Imaging.* 2019;12(5):925–7.
 80. Hickey EJ, Veldtman G, Bradley TJ, Gengsakul A, Manlhiot C, Williams WG, et al. Late risk of outcomes for adults with repaired tetralogy of Fallot from an inception cohort spanning four decades. *Eur J Cardiothorac Surg.* 2009;35(1):156–64; discussion 64.
 81. Larios G, Friedberg MK. Imaging in repaired tetralogy of Fallot with a focus on recent advances in echocardiography. *Curr Opin Cardiol.* 2017;32(5):490–502.
 82. Schafer M, Browne LP, Jagers J, Barker AJ, Morgan GJ, Ivy DD, et al. Abnormal left ventricular flow organization following repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg.* 2020;160(4):1008–15.
 83. Sjoberg P, Bidhult S, Bock J, Heiberg E, Arheden H, Gustafsson R, et al. Disturbed left and right ventricular kinetic energy in patients with repaired tetralogy of Fallot: pathophysiological insights using 4D-flow MRI. *Eur Radiol.* 2018;28(10):4066–76.
 84. Li SN, Yu W, Lai CT, Wong SJ, Cheung YF. Left ventricular mechanics in repaired tetralogy of Fallot with and without pulmonary valve replacement: analysis by three-dimensional speckle tracking echocardiography. *PLoS One.* 2013;8(11):e78826.
 85. Dragulescu A, Friedberg MK, Grosse-Wortmann L, Redington A, Mertens L. Effect of chronic right ventricular volume overload on ventricular interaction in patients after tetralogy of Fallot repair. *J Am Soc Echocardiogr.* 2014;27(8):896–902.
 86. Fernandes FP, Manlhiot C, Roche SL, Grosse-Wortmann L, Slorach C, McCrindle BW, et al. Impaired left ventricular myocardial mechanics and their relation to pulmonary regurgitation, right ventricular enlargement and exercise capacity in asymptomatic children after repair of tetralogy of Fallot. *J Am Soc Echocardiogr.* 2012;25(5):494–503.
 87. Cheung EW, Liang XC, Lam WW, Cheung YF. Impact of right ventricular dilation on left ventricular myocardial deformation in patients after surgical repair of tetralogy of fallot. *Am J Cardiol.* 2009;104(9):1264–70.
 88. Li Y, Xie M, Wang X, Lu Q, Zhang L, Ren P. Impaired right and left ventricular function in asymptomatic children with repaired tetralogy of Fallot by two-dimensional speckle tracking echocardiography study. *Echocardiography.* 2015;32(1):135–43.
 89. Firstenberg MS, Smedira NG, Greenberg NL, Prior DL, McCarthy PM, Garcia MJ, et al. Relationship between early diastolic intraventricular pressure gradients, an index of elastic recoil, and improvements in systolic and diastolic function. *Circulation.* 2001;104(12 Suppl 1):I330–5.

90. Kobayashi M, Takahashi K, Yamada M, Yazaki K, Matsui K, Tanaka N, et al. Assessment of early diastolic intraventricular pressure gradient in the left ventricle among patients with repaired tetralogy of Fallot. *Heart Vessel*. 2017;32(11):1364–74.
91. Friedberg MK, Fernandes FP, Roche SL, Grosse-Wortmann L, Manlhiot C, Fackoury C, et al. Impaired right and left ventricular diastolic myocardial mechanics and filling in asymptomatic children and adolescents after repair of tetralogy of Fallot. *Eur Heart J Cardiovasc Imaging*. 2012;13(11):905–13.
92. Cullen S, Shore D, Redington A. Characterization of right ventricular diastolic performance after complete repair of tetralogy of Fallot. Restrictive physiology predicts slow postoperative recovery. *Circulation*. 1995;91(6):1782–9.
93. Liang XC, Cheung EW, Wong SJ, Cheung YF. Impact of right ventricular volume overload on three-dimensional global left ventricular mechanical dyssynchrony after surgical repair of tetralogy of Fallot. *Am J Cardiol*. 2008;102(12):1731–6.
94. Li VW, Yu CK, So EK, Wong WH, Cheung YF. Ventricular myocardial deformation imaging of patients with repaired tetralogy of Fallot. *J Am Soc Echocardiogr*. 2020;33(7):788–801.
95. Grotenhuis HB, Dallaire F, Verpalen IM, van den Akker MJE, Mertens L, Friedberg MK. Aortic root dilatation and aortic-related complications in children after tetralogy of Fallot repair. *Circ Cardiovasc Imaging*. 2018;11(12):e007611.
96. Schafer M, Browne LP, Morgan GJ, Barker AJ, Fonseca B, Ivy DD, et al. Reduced proximal aortic compliance and elevated wall shear stress after early repair of tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2018;156(6):2239–49.