Another Step in the Right Direction

Resynchronizing the Dyssynchronous Right Ventricle Improves Its Efficiency and Function

Mark K. Friedberg, MD

Advances in the diagnosis, surgery, and management of patients with congenital heart disease (CHD) have vastly improved their survival. Of these, a representative example is tetralogy of Fallot (TOF)—a common and previously debilitating and lethal cyanotic CHD—where surgical repair in infancy or childhood has dramatically improved survival and quality of life. However, the residual anatomic and hemodynamic abnormalities associated with surgical repair of CHD, including TOF, lead to arrhythmias, exercise intolerance, heart failure, impaired quality of life, and death. The incidence of these sequelae sharply increases 3 decades after childhood repair.[1,2]

See Article by Janoušek et al

Right ventricular (RV) remodeling and failure underlie these complications and outcomes. Of the lesions created by surgical repair of CHD and TOF, long-standing, severe pulmonary regurgitation (PR) is currently considered a major cause of RV dilatation and failure. Consequently, most emphasis has been placed on the indications for, and development of, surgical and transcatheter pulmonary valve replacement for PR and outflow tract dysfunction.[3] Although pulmonary valve replacement leads to improved RV remodeling and function, its beneficial effects on exercise intolerance, arrhythmias, and sudden death are inconclusive, and a considerable proportion of patients do not adequately improve.[4]

Hence, it is apparent that PR is not the only mechanism underlying RV dysfunction and that other pathophysiological mechanisms contribute to RV failure. Among these, RV electromechanical dyssynchrony, caused by right bundle branch block (RBBB) from surgery in the proximal right bundle of His during closure of the ventricular septal defect, or in the distal bundle of His, during relief of RV outflow obstruction, is important, with relatively well-characterized and treatable pathophysiology.[5] However, although RV electromechanical dyssynchrony is common after repair of TOF and other CHD, and well recognized, it has been largely ignored as a cause of RV failure and as a therapeutic target.

In the left ventricle (LV), left bundle branch block-induced electromechanical dyssynchrony is well recognized as a contributor to LV dysfunction and heart failure. Since the mid-1990s and early 2000s, cardiac resynchronization therapy (CRT) has become a well-established and effective therapy to treat LV dysfunction in adult patients with symptomatic heart failure, LV dysfunction, and a prolonged QRS complex, especially that in a left bundle branch block pattern.[6]

Treatment of heart failure from RV dysfunction and RBBB with CRT has been less forthcoming, and no clear criteria exist. In 2014, in this journal, we reported on our results that delineated the mechanism and pathophysiology of RBBB-induced mechanical dyssynchrony in children after surgical repair of TOF.[5] In that study, using 2-dimensional, M-mode, tissue Doppler, and strain imaging echocardiography, we found that the mechanical patterns of RBBB-induced RV inefficiency mirrored those of left bundle branch block-induced LV mechanical dyssynchrony, causing a right-sided septal flash, with early apical-septal activation and concomitant prestretch of the RV basal lateral wall.[5] The regionally prestretched and hence preloaded lateral basal segment began and ended contraction late, after pulmonary valve closure (postsystolic shortening), at a time when RV contraction no longer contributes to ejection. Further worsening RV contractile inefficiency was that with strong contraction of the late-activated preloaded lateral wall and an increase in cavity pressure; there was often abrogation of the early-activated apical-septal contraction. We previously found that RV mechanical dyssynchrony and its resulting mechanical dispersion were associated with impaired exercise intolerance—a central symptom of patients after TOF repair.[7] In the LV, it is established that this typical pattern of inefficient mechanics from bundle branch block is a strong predictor of response to CRT.[8] However, to date, this had not been conclusively demonstrated for the RV.

In this issue of *Circulation: Cardiovascular Imaging*, Janoušek et al[9] report on the effects of temporary resynchronization of RV electromechanical dyssynchrony on myocardial mechanics, efficiency, and function. They study 25 patients after surgical correction of CHD, 21 of whom had TOF. Temporary RV-CRT was applied by atrial-synchronized RV free-wall pacing from 2 closely spaced electrodes near the tricuspid annulus, which is the site of latest activation in postrepair TOF patients with RBBB. They found that in all patients, RV-CRT significantly decreased QRS duration with disappearance of RBBB QRS morphology, in

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From the Labatt Family Heart Centre, Division of Pediatric Cardiology, The Hospital for Sick Children, Toronto, Ontario, Canada; and Department of Pediatrics, University of Toronto, Ontario, Canada.

Correspondence to Mark K. Friedberg, MD, Labatt Family Heart Centre, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8. E-mail mark.friedberg@sickkids.ca

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association with improved RV mechanical synchrony, efficiency, and function. Improved RV efficiency was quantified using strain-rate echocardiography as the RV systolic stretch fraction, which quantifies wasted work through the ratio of stretched versus contracting segments. Improved RV function was quantified through RV maximal+dP/dt, RV outflow tract velocity time integral (as a surrogate of stroke volume/cardiac output), and the RV myocardial performance index. Importantly, RV filling time was improved, signifying improved RV diastolic performance. Five patients underwent hemodynamic testing at the time of cardiac catheterization demonstrating that with RV-CRT, RV pressure rise was expedited and synchronized with LV pressure rise; consequently, maximum systolic RV dP/dt improved in all but one patient.

Previous authors[10–12] and now, Janoušek et al have shown that temporarily resynchronizing the dyssynchronous RV by pacing can vastly improve its mechanics, hemodynamics, and function. When a dyssynchronous, failing RV is the cause of heart failure, as is often the case in surgically repaired CHD, this is a potentially powerful tool to treat these patients.

The study by Janoušek et al is novel in delineating the effects of RV-CRT on adverse myocardial mechanics—the root cause of dyssynchronous RV failure. Several aspects of the study deserve specific attention in term of myocardial mechanics and ventricular function in relation to dyssynchrony. One of these is use of the systolic stretch fraction to demonstrate inefficient myocardial work secondary to dyssynchrony and improved efficiency with CRT. Electromechanical dyssynchrony is characterized by inefficient cardiac action because early-activated segments push blood inefficiently to stretch late-activated segments.[13] The prestretched and preloaded segments then generate force to increase cavity pressure that constitutes an insurmountable afterload on the early-activated segments; thereby terminating their contraction and contribution to ventricular output. The concept of relating stretched to contracting segments is simple, intrinsically valid, directly relates to the underlying pathophysiology, and has previously been shown to predict response to CRT in the LV.[14] Use of strain rate may speak to active myocardial force development. However, the mathematical equations presented in the article to derive the systolic stretch fraction are complex. If this concept is to translate into clinical practice, it will need to be automated or simplified. Improved ventricular efficiency is likely also the reason that the myocardial performance index improved with resynchronization because the resynchronized ventricle is able to generate pressure more rapidly in early systole and relax faster in early diastole, reducing the duration of isovolumic contraction and relaxation. The use of the myocardial performance index to delineate efficiency, rather than a nonspecific (and often noninformative) index of global ventricular function, is attractive. Nonetheless, it is informative to study the individual components of the myocardial performance index. The authors have provided the isovolumic contraction and ejection times, although not the isovolumic contraction time, which would further inform on the ability of the RV to rapidly generate pressure in early systole. The improved RV dP/dT suggests this is the case.

The second imaging point that deserves attention is the concept of shortened filling with dyssynchrony and improved filling time with CRT. Our group has demonstrated diastolic dyssynchrony and diastolic dysfunction in several conditions, including in patients with repaired TOF.[15] I think that dyssynchronous and disorganized systolic ventricular contraction is intrinsically linked to dyssynchronous and disorganized diastolic relaxation. Anecdotal inspection of regional myocardial strain curves readily shows that disorganized regional strain patterns in systole do not magically reorganize in diastole. Moreover, slow force generation in the isovolumic contraction period and postsystolic shortening of late-activated segments prolong systole, which together with an increased isovolumic relaxation period, lead to a short diastolic filling time, which is exponentially worsened in children with fast heart rates from heart failure. Improved myocardial mechanics, be it in the RV or LV, prolongs filling time allowing strengthened myocardial contraction and increased cardiac output through the Frank–Starling effect. This postulate is consistent with the recent publication from the Prague group, in a presumably overlapping population, where acute RV resynchronization in children after TOF repair improved cardiac output, blood pressure, and RV dP/dTmax.[16]

Although the current study by Janoušek et al demonstrates the potential to improve myocardial mechanics and efficiency arising from RBBB after repair of CHD, it leaves several questions unanswered. Firstly, the study's inclusion criteria, although listed, do not clarify why those patients were studied. The majority of patients (19/25) had good RV function, and it is unlikely that those patients would be candidates for permanent CRT. Only 6 patients had decreased RV function and only 2 manifested right heart failure. These are the patients most at interest for permanent RV-CRT. Twenty-three patients were studied as part of routine acute postoperative management using temporary epicardial pacing wires. The authors do not provide the rationale for routinely resynchronizing these patients. Patients with a wide spectrum of severity were studied, some intubated, some on inotropic support, some in the catheter laboratory, and some in the intensive care unit. The effects of RV pacing on the LV need to be delineated because there is the potential to introduce LV dyssynchrony and dysfunction from RV pacing. Likewise, the duration of temporary RV-CRT is not reported, and it is unknown whether the effects of pacing would be sustained. Our group has recently published on the use of sustained CRT after surgery for CHD in infants, to improve hemodynamics and potentially recovery in the intensive care unit in the first 48 hours after surgery.[17] Consistent with the current study by Janoušek et al[18] and their previous acute postoperative CRT study from 16 years ago, we showed that sustained CRT after surgery for CHD in infants improves hemodynamics in those infants with wide QRS, although we did not focus on RV failure. A partial answer to whether subpulmonary RV-CRT can be harnessed for longterm benefit comes from the 3 patients described in the current article who underwent successful permanent RV-CRT, one of whom has been previously described in a case report.[19] Thus, it is reasonable to assume that the temporary benefits in improved myocardial efficiency and function with RV-CRT can be reaped for longer

term benefit in patients with chronic right heart failure and electromechanical dyssynchrony. This will be an important topic of future investigations.

The majority of patients in the study had PR. Thus, the effects of chronic PR versus electromechanical dyssynchrony on RV myocardial function and mechanics remains unresolved. Indeed, the two may be linked in that severe RV dilatation from PR may be associated with QRS prolongation. This has important implications for treatment—whether by pulmonary valve replacement to treat PR or CRT to treat dyssynchrony. Nonetheless, the study by Janoušek et al demonstrates that in the presence of PR, myocardial efficiency and RV function improve with CRT. This suggests that regardless of PR, dyssynchrony plays a role in RV dysfunction and may be addressed through RV-CRT.

From an imaging standpoint, the article demonstrates that although RBBB is common after repair of CHD, particularly TOF, echo has a central role in investigating which patients experience mechanical inefficiency, dysfunction, and dyssynchrony who would benefit from CRT. Echocardiography will also be central to determine the response of these patients to CRT, especially because the implanted CRT device may preclude cardiac magnetic resonance imaging. Thus, electrophysiologists and echocardiographers need to work in close collaboration to investigate the effects of RBBB after repair of TOF and other CHD on RV mechanical synchrony and function, to determine who is an appropriate candidate for CRT and to follow its impact.

Now that the mechanisms and diagnosis of RV electromechanical dyssynchrony are better delineated and the beneficial impact of resynchronization on myocardial efficiency and hemodynamics has been demonstrated, RV-CRT may become a routine part of intensive care management after CHD surgery to improve postoperative hemodynamics and recovery. The question remains which patients will benefit from permanent RV-CRT after surgical repair of CHD. CRT has been shown to be beneficial in the CHD population,[20,21] but the mechanical effects of activation delay were not studied, and the role of echocardiography and RV mechanical dyssynchrony and inefficiency has not been delineated. The impact of RV electromechanical dyssynchrony and its relation to other pathophysiological mechanisms, such as PR, will need to be better delineated and criteria for candidate selection developed. Even more so than for the LV, imaging by echocardiography and other modalities, such as cardiac magnetic resonance, will play a crucial role in demonstrating the adverse effects of activation delay on RV mechanical efficiency and function, to determine candidacy for RV-CRT and to evaluate and optimize its therapeutic impact. The study by Janoušek et al is an exciting step forward in demonstrating the beneficial effects of RV-CRT on myocardial efficiency, function, and hemodynamics. This will help to introduce RV-CRT as a potentially powerful therapy, both as a temporary modality in the postoperative setting after surgical repair of CHD and especially as a sustained treatment for the dyssynchronous failing subpulmonary RV.

Disclosures

None.

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