Cardiac resynchronization therapy for pediatric heart failure

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Introduction
Cardiac resynchronization therapy (CRT) has been studied extensively and has been shown to improve quality of life and to increase survival in both ischemic and nonischemic adult heart failure patients. It has become the standard of care for symptomatic heart failure patients (New York Heart Association class III–IV) with depressed systemic ventricular function (ejection fraction <35%) and wide QRS (>120 ms) despite optimal medical therapy. The pediatric heart failure population is a heterogeneous population comprising cardiomyopathy and congenital heart disease patients. The growing number of patients surviving surgical interventions has contributed to this heterogeneity.

Current guidelines for CRT implantation in pediatric patients are broadly based on adult criteria. Pediatric patients receiving appropriate medical therapy for heart failure who have persistently poor cardiac function (measured by systemic ventricular ejection fraction) and wide QRS for age typically are referred for CRT evaluation as an alternative to cardiac transplantation. The CRT evaluation can be divided into three steps: (1) preimplant, (2) implant, and (3) postimplant. Appropriate patient selection preimplant is critically important given that use of current adult criteria for CRT implantation results in a nonresponder rate of 25% to 30%.2 Lead site selection studies, primarily conducted in adults with left bundle branch block, have shown that most patients can be successfully resynchronized from a lateral left ventricular (LV) lead. This issue has not been addressed in the pediatric population, in which isolated left bundle branch block is rare but chronic right ventricular (RV) apical pacing is common.3 Postimplant issues regarding CRT optimization, both atrioventricular (AV) and ventriculoventricular (VV), in adult and pediatric patients have been discussed, with no clear consensus. This viewpoint addresses concerns facing the pediatric electrophysiologist at each time point.

Pre-CRT implant/patient selection
For children with two ventricles and a systemic LV, the established adult criteria for CRT implantation are applicable, with minor adjustments for QRS duration. However, when confronted with complex congenital heart disease (systemic RV or univentricular hearts), there are no coherent guidelines.1 Studies suggest that the echocardiographic presence of mechanical dyssynchrony preimplant, rather than QRS duration, is an indicator for CRT response.1–3 Mechanical dyssynchrony is assessed using two-dimensional echocardiography with M-mode and more frequently with tissue Doppler imaging.2 In 2008, the American Society of Echocardiography published their consensus statement on the use of echocardiography for CRT and concluded that the preferred approach is color-coded tissue Doppler for both the assessment of LV dyssynchrony and the prediction of outcome.2

The largest multicenter study to date on the role of echocardiography in evaluating dyssynchrony is PROSPECT (Predictors of Response to CRT; abstract presented at the European Society of Cardiology Congress, September 2007).2,4 Although final results are pending, preliminary data showed that no echocardiographic measure of mechanical dyssynchrony could be used to improve patient selection. In addition, very high levels of interobserver variability (6.5%–72%) indicate a need for further refinement of both technique and methodology as a modality for diagnosing dyssynchrony.

Real time three-dimensional echocardiography also has been used in the evaluation of mechanical synchrony.5 Early reports demonstrate that this imaging modality may correctly identify segments of late contraction; however, this technology is limited by low spatial and temporal resolution, with frame rates of approximately 20 to 30 frames per second.2

Using these echocardiographic measures of dyssynchrony for patients with structurally normal hearts is challenging, even more so when evaluating patients with complex cardiac anatomy and geometry. We have used noninvasive electrocardiographic imaging (ECGI) as an objective means for measuring electrical dyssynchrony. ECGI uses 250 body surface ECGs and a patient-specific heart–torso anatomy derived from ECG-gated thoracic computed
tomography to create epicardial activation isochrones throughout the ventricle(s). The electrical dyssynchrony index is computed from the ECGI maps as the standard deviation of activation times at 500 epicardial sites on the systemic ventricle. ECGI has been successfully and reproducibly used in heart failure patients and in pediatric patients with complex congenital heart disease and has been verified by invasive catheter mapping. At our institution, patients referred for CRT evaluation routinely undergo ECGI as part of the screening process. By identifying those patients with a high electrical dyssynchrony index (indicating significant electrical dyssynchrony), we attempt to objectively preselect patients who may benefit from CRT. Implicit in this approach is the assumption that the observed mechanical dyssynchrony is largely the result of the antecedent electrical dyssynchrony. We have termed the interval between electrical activation and regional myocardial contraction as “electromechanical latency.” Using electrical dyssynchrony as a surrogate for mechanical dyssynchrony is possible only if electromechanical latency is constant throughout the ventricle.

**Implant/lead site selection**

Select placement on the LV lead at the site of latest contraction has been shown to result in greater improvement in ejection fraction and cardiopulmonary workload. In a study by Becker et al., optimal lead location was defined as the site of or the site immediately neighboring the location of the latest contraction (as determined by speckle tracking) before CRT.

Lead site selection in the pediatric population is complicated by their smaller hearts and complex coronary venous anatomy, which often accompany complex congenital heart disease. Implantation of CRT devices is complicated, especially when dealing with small hearts and complex anatomy, and often requires a team approach that includes a pediatric electrophysiologist and a pediatric cardiothoracic surgeon. Many pediatric centers electively place epicardial systemic ventricular leads. Historically, leads have been placed in a left lateral position or, if a pacing system is in place, 180° apart from the existing ventricular lead. Pre-CRT ECGI can be used to identify segments of late electrical depolarization as well as scar, lines of slow conduction, and block. In 2006, Jia et al. demonstrated that ECGI was helpful not only in determining areas of late electrical depolarization but also in identifying these other important electrophysiologic properties of the ventricle. Identifying these regions preimplant can aid in selecting a suitable location for resynchronization pacing to promote electrical synchronicity. However, electrical synchrony does not always correlate with mechanical synchrony. The delay from epicardial activation to endocardial activation, or intramural delay, may be significant in advanced heart disease and has not been systematically studied. Electromechanical latency may account for those patients who are electrically synchronous but remain mechanically dysynchronous as described by Jia et al. Although tissue Doppler imaging appears to be the ideal modality for assessing this parameter, technical obstacles and high interobserver variability have limited the utility of tissue Doppler imaging in guiding CRT lead placement. Cardiac magnetic resonance imaging also appears to be a promising imaging modality for assessing regional ventricular mechanical dyssynchrony; however, given the current state of pacemaker–magnetic resonance imaging compatibility, this modality is limited to only the preimplant phase.

**Postimplant/optimization**

Adult studies have demonstrated that many patients implanted with CRT and subsequently optimized have performed better than those patients not optimized. However, methods of optimization remain unclear and are institutional dependent.

AV optimization is routinely performed using mitral valve Doppler inflow. Measuring mitral inflow E and A waves allows for selection of the optimal AV interval, which allows for completion of atrial systole (resulting in maximal preload) while preventing mitral diastolic regurgitation. This technique has been modified for patients with congenital heart disease by measurement of systemic AV valve inflow. Interventricular (VV) optimization has remained more ambiguous. Use of tissue Doppler imaging and tissue strain imaging to minimize segmental mechanical dyssynchrony is common, but both methods are subject to image acquisition and acoustic windows. At our institution, we first acquire 12-lead ECGs under various conditions, including single ventricular site pacing (RV only, LV only) and different VV timings, to determine those intervals with more fused QRS signals. Subsequently, tissue Doppler imaging and tissue strain imaging are performed during the subset of fused VV intervals to select the interval that minimizes segmental mechanical dyssynchrony. We do not limit the scope of the echocardiographic interrogation to the narrowest QRS complex.

We have also used ECGI to assess post-CRT electrical dyssynchrony as well as changes in electrical dyssynchrony under different pacing conditions (Figure 1). This technique, first described in 2006, has repeatedly demonstrated that CRT clinical responders programmed to optimal CRT conditions have an electrical dyssynchrony index within the range of normal. Nominal CRT conditions have also shown a more normalized electrical dyssynchrony compared with single-site ventricular pacing (whether RV or LV), which consistently produces high electrical dyssynchrony indices indicating persistent dyssynchrony.

**Limitations**

One of the major limitations of ECGI is that it provides only epicardial data. Intramural delay and electromechanical latency may be quite significant, especially in diseased myocardium as seen in heart failure and structurally abnormal hearts, and may account for the population of patients who have electrical synchrony and persistent mechanical dyssyn-
chrony. Extension of ECGI to the endocardial surface will help overcome this difficulty.

Future directions

No dedicated trials to date have investigated patient selection, lead site location, or CRT optimization in the pediatric population. Given the heterogeneity of pediatric heart failure substrates, no studies have determined which substrates (if any) are more amenable to CRT. The long-term effects of pediatric CRT remain ambiguous due to the lack of longitudinal studies. The limitations of current echocardiographic techniques for patient selection, lead site selection, and optimization have been highlighted here and stress the importance of moving toward more objective methods. Noninvasive ECGI provides a safe, effective, and objective measure of electrical timing and underlying electrophysiologic substrate. In the future, the ability to create real-time patient activation isochrones may lead to a clinical role for ECGI in CRT optimization.

References


