Cardiac resynchronization therapy (CRT) is an effective treatment for adult patients with left ventricular (LV) failure. Large prospective, randomized, controlled trials have demonstrated that CRT results in improvement in cardiac function, LV reverse remodeling, decreased hospitalizations for heart failure (HF), improved quality of life, and decreased overall mortality.1-5 However, 30% of adult patients are non-responders to CRT, spurring further evaluation of electromechanical dyssynchrony to determine optimal pacing sites and to improve CRT selection criteria for maximal response.1,6

The positive response in adult HF prompted exploration of the use of CRT in pediatric HF patients. However, the effectiveness of CRT in the pediatric population is difficult to evaluate because of the complex anatomic substrates of congenital heart disease (CHD) and scar formation from multiple cardiac surgeries with a higher proportion of right bundle-branch block (RBBB) and right ventricular (RV) failure than in the adult population. The typical adult HF scenario of an LV ejection fraction (EF) ≤35% with a left bundle-branch block (LBBB) is uncommon in children; therefore, the adult selection criteria for CRT cannot be easily translated to pediatric patients. Furthermore, a small heterogeneous pediatric patient population hinders a systematic assessment of long-term benefit from CRT.

Principles of CRT

In the normal heart, ventricular electrical activation spreads through the His-Purkinje system, which has unique rapid propagation properties and widespread distribution. This allows highly coordinated electrical activation between distant regions of both ventricles, resulting in highly synchronous mechanical contraction. Given the strong relationship between electrical excitation and mechanical contraction in the myocardium, it is not surprising that abnormal electrical activation results in abnormal mechanical contraction.6,7 During a spontaneous or pacing-induced bundle-branch block, ventricular activation spreads primarily cell to cell through the surrounding myocardium, which can be up to 4 times slower than the specialized His-Purkinje system.9,10 This results in asynchronous electrical activation and thus asynchronous mechanical contraction in which opposing regions of the ventricular wall become out of phase with each other. Energy generated by contraction of early activated regions is dissipated by relaxation of late-activated regions, leading to decreased energy efficiency, depressed pump function, and deleterious ventricular remodeling.11-14

Approximately 25% of adults with HF exhibit a LBBB with mechanical dyssynchrony. CRT has traditionally targeted this electrical and mechanical dyssynchrony with biventricular pacing.15 By simultaneously pacing both ventricles, CRT uniformly prolongs the time to maximum contraction in each ventricle as the activation wave fronts from both ventricles merge.16,17 This results in a more coordinated contraction pattern, more homogeneous distribution of regional loading conditions and myocardial strain, decreased myocardial energy expenditure, and ultimately ventricular remodeling with improved pump function in CRT responders.17-22

In contrast to the adult HF population, only 9% of pediatric HF patients present with LBBB and a QRS duration (QRSd) >120 milliseconds, which likely reflects the variable causes of HF in the pediatric population.23 Pediatric HF patients, especially those with CHD, often have more variable conduction system disease secondary to surgical palliation/repair. Thus, investigators have used several pacing strategies other than the traditional biventricular systems to help restore synchrony in the various anatomic substrates of CHD, as discussed later in this review.
The first multicenter retrospective survey, published by Dubin et al in 2005, included 103 patients from 22 international institutions. CRT resulted in a significant increase in EF of 13% and a decrease in QRSd of 40 milliseconds over a median follow-up of 4 months. There were 11 non-responders, defined as those who had either no change or

Table 1. Single-Center Retrospective Studies of Permanent CRT in Pediatric and CHD-Related HF

<table>
<thead>
<tr>
<th>Study</th>
<th>Total patients, n</th>
<th>Age (range), y</th>
<th>Follow-up duration</th>
<th>CHD population, n (%)</th>
<th>Systemic RV</th>
<th>Systemic LV</th>
<th>Single ventricle</th>
<th>Primary CM</th>
<th>CCAVB</th>
<th>Conduction abnormality, n (%)</th>
<th>Type of CRT system, n (%)</th>
<th>Pre-CRT NYHA class (mean)</th>
<th>Outcomes after CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Janousek et al.</td>
<td>8</td>
<td>Median, 12.5</td>
<td>Median, 17.4 mo</td>
<td>8 (100)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Epicardial</td>
<td>2</td>
<td>↓ 45 (28)</td>
</tr>
<tr>
<td>Strieper et al.</td>
<td>7</td>
<td>Mean, 11</td>
<td>Median, 19 mo</td>
<td>7 (100)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Transvenous</td>
<td>...</td>
<td>↓ 66 (32)</td>
</tr>
<tr>
<td>Moak et al.</td>
<td>6</td>
<td>Mean, 11.3</td>
<td>Median, 10 mo</td>
<td>6 (50)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>Hybrid</td>
<td>1</td>
<td>N/A</td>
</tr>
<tr>
<td>Khairy et al.</td>
<td>13</td>
<td>Mean, 7.8</td>
<td>Mean, 16.5 mo</td>
<td>10 (76.9)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>↓ 27 (25)</td>
</tr>
<tr>
<td>Jauret et al.</td>
<td>7</td>
<td>Mean, 24.6</td>
<td>Mean, 19.4 mo</td>
<td>7 (100)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>↓ 29 (19)</td>
</tr>
<tr>
<td>Cecchin et al.</td>
<td>60</td>
<td>Median, 15</td>
<td>Median, 0.7 y</td>
<td>46 (76.7)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>↑ 40 (2)</td>
</tr>
<tr>
<td>Perera et al.</td>
<td>67</td>
<td>Unknown</td>
<td>Mean, 2.75 y</td>
<td>50 (74.6)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>↓ 10 (12)</td>
</tr>
</tbody>
</table>

AVB indicates atrioventricular block; CHD, congenital heart disease; CM, cardiomyopathy; CCAVB, congenital complete atrioventricular block; CRT, cardiac resynchronization therapy; EDD, end-diastolic diameter; EF, ejection fraction; HF, heart failure; IVCD, interventricular conduction delay; LBBB, left bundle-branch block; LV, left ventricle; NYHA, New York Heart Association; QRSd, QRS duration; RBBB, right bundle-branch block; RV, right ventricle; sysV, systemic ventricle; and VT/VF, ventricular tachyarrhythmia/ventricular fibrillation.
a decrease in their EF. Forty-six patients previously had pacemakers before upgrading to CRT, and these patients had a significant improvement in EF (by 14.5%) and decrease in QRSd (by 46 milliseconds). Of the 18 patients listed for heart transplantation, 3 were removed from the listing as a result of clinical improvement. The only difference between responders and nonresponders was a higher baseline EF in the nonresponder group. The analysis did not include...
not include the specific type of CHD as an independent variable.

Cecchin et al. published the first larger retrospective, single-center experience with pediatric and CHD CRT, which included 60 patients with CHD, 33 of whom had preexisting conventional pacemakers. With CRT, the median EF increased by 6% and the median QRSD decreased by 29 milliseconds. There was an improvement in NYHA functional class in 38% of patients with available data. Thirteen percent of patients with sufficient follow-up data were nonresponders, defined as having no improvement in NYHA functional class or <10% improvement in EF. In the patients with insufficient follow-up data, 5 patients died (8%), 2 patients underwent transplantation (3%), and 4 patients had loss of CRT functionality (7%).

The second multicenter retrospective survey, published by Janousek et al. in 2009, included 109 patients from 17 European centers. This was the first retrospective multicenter study to identify predictors for CRT responders versus nonresponders with multivariable analysis. CRT resulted in an overall improvement in EF of 11.5%, a decrease in QRSD by 30 milliseconds, a decrease in systemic ventricular end-diastolic dimension by a median of 1.1 z-scores, and an improvement in NYHA functional class over a median follow-up of 7.5 months. The majority of these patients (77%) had previous conventional pacemakers before upgrading to CRT. Of the 10 patients originally listed for heart transplantation, 4 patients were removed from the listing after CRT. The presence of a systemic LV was the strongest multivariable predictor of improvement in cardiac function with CRT. Patients with a systemic LV and prior conventional pacing-induced dyssynchrony also showed major clinical improvement and reverse LV remodeling. When patients who had concurrent cardiac surgery with CRT implementation were excluded, 18.5% of patients were nonresponders, defined as a lack of improvement in EF and NYHA functional class. Two independent predictors of nonresponse to CRT were identified: the presence of idiopathic dilated cardiomyopathy (DCM) and a poor initial NYHA functional class.

Perera et al. recently presented the largest single-center retrospective study with the longest follow-up period thus far (67 patients with a mean follow-up of 2.75 years). Forty-eight patients (72%) received conventional pacing before upgrading to CRT. There was an overall increase in EF of 10%, a decrease in QRSD by 27 milliseconds, and a decrease in systemic ventricular end-diastolic volume by 39 mL. There were 5 deaths (7%), including 2 sudden deaths, and there was an overall increased incidence of ventricular tachyarrhythmias noted with CRT (10% before CRT versus 25% after CRT). It is disturbing that the incidence of ventricular arrhythmias doubled after CRT. Whether this is the natural history of the disease or some proarrhythmia effect secondary to heterogeneous depolarization caused by CRT needs further elucidation with multicenter long-term studies.

Despite the lack of large prospective, randomized, controlled trials in the pediatric CRT literature, these retrospective studies clearly show that CRT can benefit certain subsets of patients in this heterogeneous population. The 11% to 23% nonresponse rate is substantially less than the 30% nonresponse rate seen in adult CRT patients.1,2,6,42,44–46 There are

**Figure 1.** A 12-lead ECG for a patient with tetralogy of Fallot undergoing cardiac resynchronization therapy with atrial synchronous single-site right ventricular pacing with a standard transvenous dual-chamber implantable cardioverter-defibrillator. The atrioventricular (AV) delay is adjusted to yield the narrowest QRS complex. **A,** Baseline ECG without pacing. **B,** AV delay of 120 milliseconds. **C,** AV delay of 150 milliseconds. The optimal AV delay is 150 milliseconds (C) because it yields the shortest QRS duration.
several possible explanations for this finding. The pediatric patients who have undergone resynchronization are often hand selected, and physician clinical judgment using the best available data likely played an important role in deciding which patients to resynchronize, resulting in more optimal patient selection and thus more effective response to CRT. Different substrates may also be responsible for the discrepant findings between adult and pediatric CRT response rates. Adult cardiomyopathy patients often have ischemic and infarcted tissue, which may not be electrically excitable with pacing and therefore may not be amenable to CRT. Pediatric patients may have less ischemia and more direct surgical trauma to localized regions as the source of their conduction delay, resulting in more favorable substrate amenable to resynchronization.

The current studies also demonstrate that CRT can be safely used in pediatric patients with complication rates similar to those of the adult population (10%–29%).52,44,45,47 Lead failure/dislodgement, found in 8% to 12% of patients, is the most common complication and may be related to anatomic issues in the CHD population.54,45 The 5% to 8% overall mortality rate in pediatric and CHD patients is also comparable to the 5% to 7% mortality rate reported in the adult trials.3,4,42–45

Appropriate patient identification is crucial in maximizing the effectiveness of this therapy, and further work is required to identify those who will best benefit in this complex and heterogeneous group of patients.

CRT for the Failing LV

Between 45% and 78% of pediatric and CHD patients in CRT studies have pacing-related ventricular dyssynchrony and HF.42,44,45 The multicenter study by Janousek et al45 demonstrated that patients with systemic LVs and pacing-related dyssynchrony who were upgraded to biventricular CRT had the best response, demonstrating major clinical improvement, LV reverse remodeling, and a significant decrease in QRSd. Similar results were seen in adult patients with RV pacing-induced dysfunction after upgrading to a biventricular CRT system.46,49

Another subgroup of pediatric patients with LV failure includes those with primary cardiomyopathies. Because adult DCM patients often respond well to CRT, it would be a reasonable assumption that pediatric DCM patients would also be good CRT candidates. They often have mechanical dyssynchrony by echocardiography with potential substrate amenable to resynchronization.50–53 However, Janousek et al45 demonstrated that DCM was an independent predictor of nonresponse to CRT in pediatric patients. This is in contrast to the favorable results in the adult DCM population, which demonstrated even greater improvement in systolic function, reverse remodeling, and survival than the adult ischemic cardiomyopathy population.54,55

Differences in the relationship between electrical and mechanical dyssynchrony may explain these discrepant findings. Although studies in pediatric DCM have demonstrated mechanical dyssynchrony, they have not consistently demonstrated electrical dyssynchrony.23,45,50–52 A study by Friedberg et al23 demonstrated that 65% of pediatric DCM patients had mechanical dyssynchrony by echocardiography; however, the median QRSd was only 84 milliseconds, and the degree of mechanical dysynchrony did not correlate with QRSd. Another study by Chen et al13 showed that 18% of DCM patients have a QRSd >120 milliseconds, but the average QRSd for their entire cohort of 89 DCM patients was only 93 milliseconds. They also found that QRSd did not correlate with intraventricular mechanical dyssynchrony.

This is in contrast to studies in adult DCM patients demonstrating average QRSd >150 milliseconds, with no correlation with intraventricular mechanical dyssynchrony.54–56 This difference highlights the importance of understanding the relationship between electrical and mechanical dyssynchrony to optimize patient selection criteria for CRT and to improve response to CRT.

CRT for the Failing RV

RV HF is an important cause of late morbidity in CHD.57 Thus, it is not surprising that >70% of CRT in the pediatric age group has been in the setting of CHD, with 30% to 40% involving the RV.42,44,45 The cause of RV dysfunction in CHD may be chronic pressure overload, volume overload, myocardial injury/scar associated with cardiopulmonary bypass or surgical repair, or a combination of these factors.

Patients with repaired tetralogy of Fallot commonly develop RBBB associated with ventricular septal defect repair, RV myocardial scar from cardiac surgeries, and RV volume or pressure overload secondary to pulmonary regurgitation or stenosis, ultimately resulting in RV failure. Several studies have demonstrated electrical and mechanical dyssynchrony in this population, suggesting a substrate for resynchronization.58–60

It has been hypothesized that RV pacing in patients with RBBB can create an activation wave front that moves in the opposite direction of the spontaneously occurring activation wave front. Manipulating the atrioventricular interval appropriately can allow merging of the intrinsic activation originating from the native left bundle with the wave front created from the RV pacing lead, resulting in more synchronous electrical activation and a shorter QRSd (Figure 1). This concept involves atrial synchronous single-site pacing only from the RV, rather than the traditional biventricular pacing concept used in adult CRT.

Initial studies in children evaluated the acute hemodynamic effects of this resynchronization concept.61–63 In 2001, Janousek et al61 used temporary epicardial pacing wires in 7 postoperative CHD patients with 2-ventricle anatomy and RBBB. Intraventricular resynchronization was successfully achieved with atrial synchronous RV pacing from the lateral RV wall. The atrioventricular delay was manipulated to apply the RV pacing stimulus synchronously with the native ventricular depolarization, resulting in maximum QRSd shortening and increased systolic blood pressure. In 2003, Dubin et al62 used transvenous catheters for atrial synchronous single-site RV pacing in 7 patients with RBBB and RV dysfunction. Atrioventricular sequential pacing was performed from 3 different RV pacing sites (apex, outflow tract, septum) with the use of an atrioventricular interval that allowed maximum fusion with the intrinsic electrical activation wave front. This resulted in decreased QRSd, improved RV dP/dtmax, and increased cardiac output, with a strong relationship between the degree of QRS narrowing and the...
increase in cardiac output. Interestingly, the optimal RV pacing site varied between patients, and the site that resulted in the narrowest QRS duration did not correlate with the site yielding the optimal RV function.

With these promising acute results, CRT with long-term single-site RV stimulation has been proposed as a treatment for RV failure. In 2008, Dubin et al.64 conducted a pilot prospective, single-blind, crossover study in patients with tetralogy of Fallot and RV failure who already had a standard dual-chamber implantable cardioverter-defibrillator (ICD) in place. Six patients were evaluated at baseline, after 3 months of CRT with atrial synchronous single-site RV pacing, and after 3 months without pacing. Results demonstrated improved RV EF and functional status with single-site RV resynchronization without compromising LV function.

These studies show that although single-site RV pacing in a patient without a bundle-branch block is potentially detrimental, it can be beneficial in patients with RV failure and RBBB with optimal manipulation of the atrioventricular delay for maximal electrical resynchronization. Single-site RV pacing has the advantage of being technically straightforward for implantation, but it may be difficult to maintain a stable degree of electrical fusion as a result of variations in intrinsic atrioventricular conduction over a wide range of activities and heart rates. In addition, a significantly prolonged baseline PR interval may prevent fusion between the paced and physiological activation resulting from limitations in the maximum programmable atrioventricular interval on pacemaker devices. In such cases, CRT with biventricular pacing may be necessary.

Thambo et al.65,66 evaluated short- and long-term effects of biventricular CRT in adult tetralogy of Fallot patients with RV dysfunction. Biventricular stimulation decreased QRS duration and improved biventricular contractility at short-term follow-up.66 Six months of biventricular CRT demonstrated improvement in exercise tolerance, NYHA functional class, ventricular synchrony, and LV EF.65 Therefore, although biventricular stimulation may involve a more difficult implantation process, it allows more consistently homogeneous ventricular activation when resynchronization of the failing RV with isolated RV pacing is not feasible or if concomitant LV dysfunction is present.

Up to one third of patients with systemic RVs, including congenitally corrected transposition of the great arteries and complete transposition of the great arteries with intra-atrial baffles, will also develop RV dysfunction.67,68 Technical feasibility and benefits of CRT in this population were evaluated by Janousek et al.37 in 2004 (Table 3). Six of the 8 patients (75%) had conventional pacing systems with LV pacing-induced conduction delay and prolonged QRS duration. CRT was achieved by atrial synchronous simultaneous biventricular pacing, resulting in decreased QRS duration, interventricular mechanical delay, and improvement in RV function.

Results in subsequent studies, however, demonstrated mixed results for patients with systemic RVs (Table 3). The multicenter study by Dubin et al.44 included 17 patients with systemic RVs. Twelve patients had a significant improvement in systemic RV EF with a decrease in QRS duration and clinical improvement. In contrast, Cecchin et al.42 reported a poor response in patients with systemic RVs, with only 2 of their 9 patients demonstrating improvement with CRT. The multicenter study by Janousek et al.45 demonstrated a modest improvement in EF, QRS duration, and NYHA functional class in 27 patients with systemic RVs. However, this response was significantly less pronounced than the positive response seen in the 62 patients with systemic LVs.

The smaller benefit of CRT in the systemic RV population may be attributed to suboptimal myocardial fiber arrangement and abnormal ventricular contraction patterns compared with both subpulmonary RVs and systemic LVs, as well as

### Table 3. Studies That Reported Response to CRT in Patients With Systemic Right Ventricles

<table>
<thead>
<tr>
<th></th>
<th>Janousek et al.,37 2004</th>
<th>Dubin et al.,44 2005</th>
<th>Cecchin et al.,42 2009</th>
<th>Janousek et al.,45 2009</th>
<th>Jauvert et al.,41 2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients with systemic RVs, n</td>
<td>8</td>
<td>17</td>
<td>9</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Age (range), y</td>
<td>Median, 12.5 (6.9–29.2)</td>
<td>Median, 12.7 (4.9–50)</td>
<td>Median, 27 (0.5–43)</td>
<td>Median, 28.8 (mean)</td>
<td>Mean, 24.6 (15–50)</td>
</tr>
<tr>
<td>Follow-up duration (range), mo</td>
<td>Median, 17.4</td>
<td>Median, 4</td>
<td>Median, 8.4</td>
<td>Median, 7.3</td>
<td>Mean, 19.4</td>
</tr>
<tr>
<td>CRT pacing method, n</td>
<td>7 BIV</td>
<td>BIV</td>
<td>BIV</td>
<td>26 BIV</td>
<td>BIV</td>
</tr>
<tr>
<td>BiV</td>
<td>1 multisite RV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-CRT QRSd, ms</td>
<td>161±21</td>
<td>...</td>
<td>Median, 165</td>
<td>Median, 160</td>
<td>160±31</td>
</tr>
<tr>
<td>Pre-CRT systV EF, %</td>
<td>...</td>
<td>...</td>
<td>Median, 28</td>
<td>28±±10</td>
<td>...</td>
</tr>
<tr>
<td>Pre-CRT NYHA FC</td>
<td>Mean, 2</td>
<td>...</td>
<td>Median, 2</td>
<td>Mean, 3</td>
<td></td>
</tr>
<tr>
<td>Outcomes after CRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in QRSd, ms</td>
<td>↓ 45</td>
<td>↓ 38.2±29.4</td>
<td>↓ 15</td>
<td>↓ 21</td>
<td>120±28</td>
</tr>
<tr>
<td>(mean)</td>
<td>(mean±SD)</td>
<td>(median)</td>
<td>(median)</td>
<td>(mean±SD)</td>
<td></td>
</tr>
<tr>
<td>Change in systV EF units</td>
<td>↑ 4</td>
<td>↑ 13.3±11.3</td>
<td>↑ 14</td>
<td>↑ 7.2±9.9</td>
<td>...</td>
</tr>
<tr>
<td>(mean)</td>
<td>(mean±SD)</td>
<td>(median)</td>
<td>(median)</td>
<td>(mean±SD)</td>
<td></td>
</tr>
<tr>
<td>NYHA improvement</td>
<td>Mean, ↓ 0.7 FC</td>
<td>...</td>
<td>...</td>
<td>Mean, ↓ 1 FC</td>
<td>Mean, ↓ 1.4 FC</td>
</tr>
<tr>
<td>Clinical improvement, n (%)</td>
<td>8/8 (100)</td>
<td>13/17 (76.5)</td>
<td>2/8 (25)</td>
<td>19 (86.4)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Nonresponders (%N)</td>
<td>...</td>
<td>4/17 (23.5)</td>
<td>6/8 (75)</td>
<td>3/22 (13.6)</td>
<td>...</td>
</tr>
</tbody>
</table>

BIV indicates biventricular; CRT, cardiac resynchronization therapy; EF, ejection fraction; FC, functional class; NYHA, New York Heart Association; QRSd, QRS duration; RV, right ventricle; and systV, systemic ventricle.
decreased myocardial perfusion reserve, possibly resulting in chronic subendocardial ischemia.59–74

**CRT for the Failing Single Ventricle**
Despite an improvement in survival rates for patients with single-ventricle physiology, these patients remain at high risk for postoperative myocardial dysfunction.75 The cause of the ventricular dysfunction is unclear but may be related to inadequate myocardial protection, multiple scars, chronic volume and pressure loads, or ventricular morphology.76–79 Traditional HF therapies such as inotropic support come at the price of increased myocardial consumption, altered hemodynamics, and adverse mechanical energetics.

Because patients with single-ventricle physiology, by definition, do not have 2 separate ventricles, resynchronization must be achieved by “multisite” pacing of the functionally single ventricle. This strategy of multisite pacing was first evaluated by Zimmerman et al80 and later by Bacha et al81 in the immediate postoperative setting. Three unipolar temporary epicardial pacing leads were placed as far apart from each other on the ventricle as possible to allow simultaneous stimulation of both free walls. Both studies demonstrated that multisite ventricular pacing acutely resulted in improvement in systolic blood pressure, cardiac index, indexes of dyssynchrony by echocardiography, and QRSd. It is interesting to note that although the baseline QRSd was normal, multisite pacing further narrowed the QRSd in both studies.

There have been no dedicated studies evaluating the effect of long-term CRT in single-ventricle patients, although 3 studies have included a small number of these patients with mixed results (Table 4).42,44,45 The study by Cecchin et al42 included 13 single-ventricle patients, 8 of whom had previous conventional pacemakers because of complete heart block. Eight of the 13 patients had an improvement in NYHA classification by 2 to 3 points or increased EF of ≥10 units. The median baseline QRSd in was prolonged at 129 milliseconds and decreased with multisite pacing to 116 milliseconds. The median baseline EF was 37%, which improved to 47% with multisite CRT. There was an overall positive response to CRT in 10 of 11 of the patients with long-term follow-up. Two single-ventricle patients died: 1 patient died of progressive HF, and 1 patient died suddenly and unexpectedly despite improvement both clinically and echocardiographically.

Janousek et al43 also demonstrated improvement in NYHA functional class with multisite CRT in 3 of the 4 single-ventricle patients included in their retrospective, multicenter study. Two of the 3 positive responders had prior conventional pacing. Dubin et al,44 however, did not find as promising results, with clinical improvement in only 2 of 7 single-ventricle patients included in their multicenter retrospective study despite a significant decrease in mean QRSd by 45 milliseconds.

The inconsistent response to multisite CRT is likely a reflection of the complex and heterogeneous structural abnormalities in this population. A better understanding of electrical and mechanical interactions in single ventricles will be important for optimal lead placement to maximize CRT response, and an individualized approach will likely be required, depending on the anatomic substrate.

**Patient Selection and Lead Placement for CRT**
There are currently no accepted consensus guidelines for implementation of CRT in pediatric HF patients. Adult selection guidelines (Class I, Level of Evidence A: LV EF ≤35%, QRSd ≥150 milliseconds with LBBB morphology, and NYHA class III–IV despite optimal medical therapy) are difficult to apply to the pediatric population in which systemic RV failure and RBBB are more prevalent because of the large proportion of HF related to CHD.82 Only 9% of pediatric and CHD patients who have undergone resynchronization have systemic LV failure and LBBB.43 A minority of the patients receiving CRT (32%–38%) had a baseline NYHA class III to IV; furthermore, an initially poor NYHA class was a predictor of nonresponse to CRT.42,44,45 In addition, NYHA class poorly correlates with EF in pediatric and CHD patients and therefore may not be an appropriate indication for CRT in this population.43

| Table 4. Studies That Reported Response to CRT in Patients With Single Ventricles |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | Dubin et al44   | Cecchin et al42 | Janousek et al43 |
| Total patients single ventricles, n | 2005           | 2009           | 2009           |
| Median age (range)              | 3.1 y (5 mo–23.7 y) | 17.3 y (0.5–42.5 y) | 10.3 y (3.7–30.3 y) |
| Conventional pacing before CRT, n (%) | ...          | 8 (61.5)       | 3 (75)         |
| Median pre-CRT QRSd, ms         | ...            | 129            | ...            |
| Median pre-CRT EF, %            | ...            | 37             | ...            |
| Outcomes after CRT              |                |                |                |
| Change in QRSd, ms              | ↓ 44.8±26.2 (mean) | ↓ 13 (median) | ...            |
| Change in EF units              | No change (median) | ↑ 11 (median) | ...            |
| Clinical improvement, n (%)     | 2 (28.6)       | 10 (90.9)      | 3 (75)         |
| Nonresponders, n (%)            | 5 (71.4)       | 1 (9.1)        | 1 (25)         |

CRT indicates cardiac resynchronization therapy; EF, ejection fraction; and QRSd, QRS duration.
The aforementioned studies demonstrate that the majority (42%–77%) of pediatric patients receiving CRT have pacing-induced dyssynchrony from conventional pacing. These patients typically respond well to CRT, especially when there is a systemic LV present.42–45 Meanwhile, 12% to 33% of pediatric patients receiving CRT have systemic RVs and have demonstrated mixed results. So what markers can be used to predict response to CRT and to improve patient selection?

Although adult trials and guidelines use a prolonged QRSd as a criterion for CRT, several adult studies demonstrated that QRSd poorly predicts response to CRT and that mechanical dyssynchrony by echocardiography was a better predictor of response to CRT.83–85 In addition, adult patients with HF and dyssynchrony by echocardiography was a better predictor of QRSd poorly predicts response to CRT and that mechanical dyssynchrony alone is not likely to be a strong predictor of response to CRT.

Typically, electrical dyssynchrony and mechanical dyssynchrony are thought to be tightly coupled; however, in the pediatric population where a multitude of anatomic abnormalities and pressure/volume loads can alter cardiac myocyte structure and contraction patterns, mechanical and electrical dyssynchrony may not always be related. Motonaga et al91 demonstrated that patients with hypoplastic left heart syndrome and preserved RV function have mechanical dyssynchrony by echocardiography but no evidence of electrical dyssynchrony by QRSd or 3-dimensional electroanatomic activation mapping. In addition, RV failure appears to correlate with electrical dyssynchrony measured by QRS prolongation but not with indexes of mechanical dyssynchrony by echocardiography in these patients.92 This highlights the importance of how abnormal mechanical activation should be interpreted in the pediatric and CHD population.

Kass93 raised this issue in adult HF, commenting that the mechanical dyssynchrony found in 30% to 70% of that population may reflect the heterogeneity of myocardial contractile properties rather than delayed electrical activation. Weaker regions of the ventricular wall (secondary to ischemic damage, hypoperfusion, fibrosis, etc) may contract more weakly than stronger regions, leading to discordant wall motion as the stronger segment causes the weaker segment to move paradoxically. The anatomic abnormalities, surgical scars, and chronic pressure/volume loads commonly seen in CHD may certainly explain abnormal myocardial contraction unrelated to electrical activation. Therefore, the mechanical dyssynchrony identified in the various subtypes of pediatric heart disease may not always be amenable to correction by CRT, and mechanical dyssynchrony alone is not likely to be a strong predictor of response to CRT.

Innovative tools such as ECG imaging and 3-dimensional electroanatomic mapping enable a far more detailed analysis of electrical activation than the standard 12-lead ECG (Figure 2).94–96 These modalities, combined with advanced echocardiographic evaluation of mechanical dyssynchrony such as color tissue Doppler imaging and 3-dimensional echocardiography, can be used to better understand the relationship between electrical and mechanical dyssynchrony. Direct comparison of electrical activation patterns with patterns of mechanical dyssynchrony will be important in understanding electromechanical interactions to improve patient selection and to optimize pacing strategies for maximal response to CRT.

**CRT Combined With ICD**

The use of CRT combined with ICD (CRT-D) in pediatric/CHD HF patients is complex because of the heterogeneity of the population and requires a larger discussion outside the scope of this review. There are no published studies evaluating the use of CRT-D versus CRT alone in this population. However, it is well known that certain subsets of patients with CHD are at risk of sudden death and HF and therefore could potentially benefit from CRT-D.97–99 With a lack of studies to support consensus statements about the use of CRT-D in this heterogeneous population, the decision to use CRT-D versus CRT alone must be made with an individualized approach. The patient’s individual risk of arrhythmias and sudden death must be weighed carefully against the known risk of inappropriate ICD shocks, which was 20% in a large retrospective, multicenter study of ICDs in the pediatric and CHD population.100 In addition, the increased incidence of ventricular tachyarrhythmias noted with CRT in the retrospective study by Perera et al93 raises the question of whether CRT results in a proarrhythmia effect, and if so, perhaps CRT-D would be more beneficial than CRT alone. Multicenter long-term studies are required to further elucidate this issue.

**CRT Implantation Issues in Pediatric Heart Disease and CHD**

Implantation of a CRT system can be challenging in pediatric patients. Patients with relative or absolute contraindications to a transvenous approach such as abnormal venous anatomy, single ventricles, tricuspid valve abnormalities/protheses, or intracardiac shunts require an epicardial approach. For patients who already have a traditional epicardial pacing system in place and are being upgraded to a biventricular CRT system, the epicardial LV lead can be placed through a mini-sternotomy, although scarring from previous surgeries or structural abnormalities in CHD may make access to the LV difficult from this approach (Figure 3). An alternative strategy is to implant the epicardial LV lead via a mini-thoracotomy.101 The additional LV lead can then be tunneled to the existing pacemaker pocket.

For patients with normal intracardiac anatomy and an existing transvenous pacing system, there are several strategies for upgrading to a biventricular CRT system. If the patient is large enough to accommodate a completely transvenous system, the additional LV lead can be placed transvenously in the coronary sinus (Figure 4). In patients with abnormal or small coronary sinus anatomy or venous obstruction in the
presence of a conventional transvenous system, an LV lead can be placed epicardially, through a mini-sternotomy or mini-thoracotomy, to create a hybrid biventricular CRT system (Figure 5).

For patients without a preexisting pacing system, the decision to place a transvenous versus epicardial CRT system will depend on multiple factors. Those anatomic abnormalities that preclude a transvenous system will require a completely epicardial CRT system. Placement of an epicardial CRT system may be complicated by previous sternotomies and scaring from prior surgeries, which make gaining access to the epicardium difficult and can result in higher pacing and sensing thresholds, lead failure, and earlier battery depletion rates.102,103

In addition to limitations related to anatomic abnormalities from CHD, the decision to place a transvenous versus epicardial CRT system is limited by other factors unique to the pediatric population. Patient body size, venous diameter, and coronary sinus size may limit the use of a transvenous CRT system. Pediatric patients experience a significant amount of growth, which requires careful consideration when a transvenous CRT system is placed. An inadequate amount of lead length to accommodate growth may result in lead dislodgement, lead fracture, or distortion of the tricuspid valve. It is also critical to realize that these patients will require a pacing system for many decades and therefore may require multiple lead replacements over time. Placing transvenous leads in young children may result in vessel occlusion, making future

Figure 2. Three-dimensional electroanatomic activation mapping of the right ventricle (RV) in patients with a normal heart (A and B), tetralogy of Fallot (TOF; C and D), and hypoplastic left heart syndrome (HLHS; E and F). The normal RV has the earliest electrical activation seen in the distal third of the ventricular septum with propagation of depolarization spreading to the apex and subsequently to the base and outflow tract. The HLHS patient has an electrical activation pattern similar to that of the patient with a normal heart. However, the TOF patient has an abnormal electrical activation pattern with the latest electrical activation seen at the RV free wall.
transvenous lead placements impossible without lead extractions. Other issues to consider in pediatric patients include limitations of device programmability. Maximum upper tracking rates and minimum atrioventricular interval programming options will be manufacturer dependent and may be suboptimal for younger pediatric patients who have higher heart rate ranges and require shorter atrioventricular intervals for CRT.

Conclusions

CRT can be a powerful tool for treating HF in pediatric and CHD patients. However, there are currently no accepted consensus guidelines for patient selection criteria for implementation of CRT in this population, and the adult selection criteria for CRT cannot be easily applied. The mixed results of CRT for certain anatomic substrates demonstrated in the current literature reflects the need for further understanding of the relationship between electrical and mechanical dyssynchrony. New innovative tools may provide a more detailed analysis of dyssynchrony to aid in this endeavor. The heterogeneity of this population will likely require somewhat individualized approaches to the selection process and pacing strategy for optimal CRT response.

Disclosures

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References


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Supplemental Table 1. Case reports for permanent cardiac resynchronization therapy in pediatric and congenital heart disease related heart failure.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Age</th>
<th>Population</th>
<th>Pre-CRT Pacing</th>
<th>QRS</th>
<th>F/U</th>
<th>Change in QRS&lt;br&gt;units</th>
<th>Change in sysV&lt;br&gt;EF units</th>
<th>Pre-CRT NYHA</th>
<th>Post-CRT NYHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez-Cruz et al 2001</td>
<td>1</td>
<td>24 yo</td>
<td>Systemic RV (ccTGA)</td>
<td>Y</td>
<td>--</td>
<td>1 mo</td>
<td>--</td>
<td>--</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>Roofthooft et al 2003</td>
<td>1</td>
<td>3 mo</td>
<td>Systemic LV (SubAS, CoA, VSD)</td>
<td>Y</td>
<td>LBBB</td>
<td>6 mo</td>
<td>↓ 20 ms</td>
<td>↑ 20</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Blom et al 2003</td>
<td>1</td>
<td>6 yo</td>
<td>Systemic LV (VSD, MVR)</td>
<td>N</td>
<td>LBBB</td>
<td>12 mo</td>
<td>↓ 40 ms</td>
<td>↑ 11</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Senzaki et al 2004</td>
<td>1</td>
<td>18 yo</td>
<td>Single RV (asplenia, AVC)</td>
<td>N</td>
<td>RBBB</td>
<td>Acute</td>
<td>--</td>
<td>↑ 21</td>
<td>IV</td>
<td>II</td>
</tr>
<tr>
<td>Janousek et al 2004</td>
<td>1</td>
<td>3.4 yo</td>
<td>Systemic LV (PCM, CCAVB)</td>
<td>Y</td>
<td>LBBB</td>
<td>1 mo</td>
<td>--</td>
<td>--</td>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td>Cowburn et al 2005</td>
<td>1</td>
<td>41 yo</td>
<td>Systemic RV (d-TGA)</td>
<td>Y</td>
<td>RBBB</td>
<td>6 wks</td>
<td>↓ 50 ms</td>
<td>↑ 20</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Kakavand et al 2006</td>
<td>1</td>
<td>32 yo</td>
<td>Systemic RV (ccTGA)</td>
<td>Y</td>
<td>--</td>
<td>Acute</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>van Beek et al 2006</td>
<td>3</td>
<td>1.5 yo</td>
<td>PCM/CCAVB</td>
<td>Y</td>
<td>25 mo</td>
<td>↓ 60 ms</td>
<td>↑ 32</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>1.5 yo</td>
<td>Systemic LV (d-TGA)</td>
<td>Y</td>
<td>21 mo</td>
<td>↓ 40 ms</td>
<td>↑ 45</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>23 yo</td>
<td>VSD</td>
<td>Y</td>
<td>35 mo</td>
<td>↓ 40 ms</td>
<td>↑ 21</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Chen et al 2007</td>
<td>1</td>
<td>3 yo</td>
<td>Idiopathic DCM</td>
<td>N</td>
<td>LBBB</td>
<td>3 mo</td>
<td>--</td>
<td>↑ 22</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Gonzalez et al 2009</td>
<td>1</td>
<td>8 yo</td>
<td>Idiopathic DCM</td>
<td>N</td>
<td>--</td>
<td>10 mo</td>
<td>↓ 30 ms</td>
<td>↑ 33</td>
<td>II-III</td>
<td>I</td>
</tr>
<tr>
<td>Ortega et al 2012</td>
<td>1</td>
<td>10 mo</td>
<td>Systemic LV (DORV)</td>
<td>Y</td>
<td>--</td>
<td>3 mo</td>
<td>↓ 30 ms</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hauser et al 2013</td>
<td>1</td>
<td>20 mo</td>
<td>Systemic LV (DCM/myocarditis)</td>
<td>N</td>
<td>--</td>
<td>24 mo</td>
<td>--</td>
<td>↑ 30</td>
<td>III</td>
<td>I</td>
</tr>
</tbody>
</table>

sysV = systemic ventricle, ccTGA = congenitally corrected transposition of the great arteries, SubAS = subaortic stenosis, CoA = coarctation, VSD = ventricular septal defect, MVR = mitral valve replacement, AVC = Atrioventricular canal, PCM = pacemaker induced cardiomyopathy, CCAVB = congenital complete atrioventricular block, DCM = dilated cardiomyopathy, DORV = double outlet right ventricle.
Supplemental References:


8. van Beek E, Backx A, Singh S. Cardiac resynchronization as therapy for congestive cardiac failure in children dependent on chronic cardiac pacing. *Cardiol Young*. 2006;16:187-189


