Resynchronization Therapy in Pediatric and Congenital Heart Disease Patients

An International MultiCenter Study

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OBJECTIVES
Our objective was to evaluate the short-term safety and efficacy of cardiac resynchronization therapy (CRT) in children.

BACKGROUND
Cardiac resynchronization therapy has been beneficial for adult patients with poor left ventricular function and intraventricular conduction delay. The efficacy of this therapy in the young and those with congenital heart disease (CHD) has not yet been established.

METHODS
This is a multi-center, retrospective evaluation of CRT in 103 patients from 22 institutions.

RESULTS
Median age at time of implantation was 12.8 years (3 months to 55.4 years). Median duration of follow-up was four months (22 days to 1 year). The diagnosis was CHD in 73 patients (71%), cardiomyopathy in 16 (16%), and congenital complete atrioventricular block in 14 (13%). The QRS duration before pacing was 166.1 ± 33.3 ms, which decreased after CRT by 37.7 ± 30.7 ms (p < 0.01). Pre-CRT systemic ventricular ejection fraction (EF) was 26.2 ± 11.6%. The EF increased by 12.8 ± 12.7 EF units with a mean EF after CRT of 39.9 ± 14.8% (p < 0.05). Of 18 patients who underwent CRT while listed for heart transplantation, 3 improved sufficiently to allow removal from the transplant waiting list, 5 underwent transplant, 2 died, and 8 others are currently awaiting transplant.

CONCLUSIONS
Cardiac resynchronization therapy appears to offer benefit in pediatric and CHD patients who differ substantially from the adult populations in whom this therapy has been most thoroughly evaluated to date. Further studies looking at the long-term benefit of this therapy in this population are needed. (J Am Coll Cardiol 2005;46:2277–83) © 2005 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) using biventricular pacing has been shown to be a beneficial therapy in adults with left ventricular dysfunction and intraventricular conduction delay (1–7). In patients with left ventricular failure and left bundle-branch block, CRT has produced acute hemodynamic improvement in left ventricular performance (4,5). In more chronic application, CRT has been shown to improve exercise tolerance and heart failure symptoms, and most recently to improve survival (1,3,7). The efficacy of CRT in children and in older patients with...
congenital heart disease (CHD) has not been established, and comprises the subject of this report.

Several studies of CRT in patients after surgery for congenital heart defects have shown that CRT improves hemodynamics (8,9). Chronic biventricular CRT in this population is the subject of case reports and several small studies (8–15). Thus, it is not known whether the pediatric experience will resemble that seen with adults, as the patient substrate differs markedly from adult patients. Therefore, the objective of this study was to review a multi-center experience with CRT in pediatric patients and those with CHD.

**METHODS**

This study is a retrospective investigation that was initiated through the Pediatric Electrophysiology Society. Twenty-two centers in the U.S., Canada, and Europe participated (see online Appendix). Members of the Society were asked to report on the indications, outcomes, and complications for all patients who received biventricular CRT and were under 21 years of age, or who had CHD regardless of age. Institutional review board approval to report this data was obtained from each site. Data collected included underlying heart disease, indication for implant, measurements of clinical status (New York Heart Association [NYHA] functional class or Ross status as reported by site physician) and cardiac function (using echocardiogram or radionuclide scan), as well as clinical outcome (16).

Values are expressed as either median (range) or mean (± SD) depending on the distribution of the data. Categorical variables were evaluated by chi-square analysis. Continuous variables were evaluated by analysis of variance and two-tailed t tests. Relationships between continuous variables were explored using univariate linear regression.

**RESULTS**

**Patients.** Devices capable of biventricular CRT were implanted in 103 patients <21 years of age or with CHD. The median age at CRT implantation was 12.8 years (3 months to 55.4 years) as shown in Figure 1. There were 17 patients over 21 years of age, all of whom had CHD. There were 11 patients less than one year old. Overall, 73 (71%) patients had CHD, 16 (16%) had cardiomyopathy, and 14 (13%) had congenital complete atrioventricular block. Thirty-nine patients were reported to be NYHA functional class 3 or 4 before CRT; 15 patients were reported to be NYHA class 1.

**Table 1.** Patient Therapies Before and After CRT Pacemaker Placement

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Pre-CRT</th>
<th>Post-CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>Diuretics</td>
<td>59</td>
<td>56</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>66</td>
<td>70</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>31</td>
<td>38</td>
</tr>
<tr>
<td>Positive inotropic agents</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>ECMO/LVAD</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; CRT = cardiac resynchronization therapy; ECMO = extracorporeal membrane oxygenation; LVAD = left ventricular assist device.

**Figure 1.** Histogram of age distribution of patients who received cardiac resynchronization therapy therapy.

Congenital heart disease diagnoses included: left-sided obstructive lesions (n = 15); l-transposition of the great arteries with systemic right ventricular failure (n = 12); tetralogy of Fallot or variant lesion (n = 11); atrioventricular canal defect (n = 10); d-transposition of great arteries (n = 12); and other (n = 13). Single ventricle physiology was present in seven patients. Pacemakers had previously been implanted in 27 patients because of surgical atrioventricular pacing in 11 patients and dual-chamber pacing in 14 patients.

There were 16 patients with cardiomyopathy, including 10 with dilated cardiomyopathy; 4 with hypertrophic cardiomyopathy; 1 with a metabolic myopathy; and 1 with Duchenne’s muscular dystrophy. Pacemakers had previously been implanted in six of these patients for a median of 4.3 years (0.8 months to 5.1 years) before upgrade to CRT with ventricular pacing.

Fourteen patients had congenital complete atrioventricular block with a median age of 12.5 years (3 months to 24.3 years). Ten were previously paced with dual-chamber (atrioventricular) systems, and three were paced only with ventricular leads before CRT. One patient received CRT as primary therapy. These patients were paced a median of 5.3 years (3 months to 17.7 years) before upgrade to CRT.

Of the total population, 96 were taking at least one heart failure medication, and 6 patients were dependent on positive inotropic agents. Table 1 lists details of the medications taken and support required before placement of a device.
biventricular system. There were 18 patients who were listed for heart transplantation.

**Systems.** In 45 patients, a transvenous CRT placement was performed; in 48, the system was epicardial; and in 10 patients a mixed system was used (Fig. 2). Mixed systems were used exclusively in CHD patients. Patients receiving epicardial systems were younger than those who received transvenous systems (4.6 vs. 16.9 years, p < 0.05). Implantable cardioverter-defibrillator (ICD) capability was included in 20 devices; of these, 6 were in patients with cardiomyopathy, and 14 were in patients with CHD (Table 2). The median age at implant for a CRT/ICD system was 17.2 years (9 to 55.4 years), which was significantly older when compared with the rest of the group: 11.5 years (4 months to 51.4 years), (p < 0.05). However, ejection fraction (EF) was similar between the groups (26.6 ± 11.7% for the CRT group vs. 23.7 ± 10.8% for the CRT/ICD group).

**Clinical status.** Follow-up data were obtained 4.8 ± 4 months after initiation of CRT. In the 94 patients with data available, the mean QRS duration before CRT was 166 ± 33 ms, which decreased to 126 ± 24 ms after CRT (p < 0.01). Ejection fraction before and after CRT was available in 89 patients (74 by echocardiography and 14 by radionuclide scan). The mean EF of the systemic ventricle before CRT was 26.2 ± 12%, which increased by 13 ± 13 EF units (p < 0.05). The EF after CRT was 40 ± 15%. Fifty-six patients met adult criteria for CRT with an EF ≤35% and a QRS duration of ≥120 ms. No relationship could be found between baseline EF or QRS duration and EF improvement.

Table 1 shows medical support required after biventricular pacemaker placement. Of the six patients on intravenous positive inotropic agents before CRT placement, five were weaned from this support after implantation. Of 18 patients listed for transplantation at the time of CRT, 3 improved and were removed from active listing, 5 underwent transplant, 2 died, and 8 are currently awaiting transplant.

**Upgrade of pacemaker to CRT.** Forty-six patients had previous pacemaker systems in place before upgrade to CRT. These systems were in place a median of 6.0 years (24 days to 35.5 years) before upgrade to CRT. These patients had a significant improvement in EF with CRT therapy (14.5 ± 11.4 EF units) (p < 0.05). They also had a significant decrease in QRS duration of 46.2 ± 36.1 ms (p < 0.05). No significant differences in age of patients, baseline EF, or change in EF were seen comparing those who had prior pacemaker therapy with those who did not.

Table 2. Type of CRT System and Adverse Events by Type of Heart Disease

<table>
<thead>
<tr>
<th>Type of Heart Disease</th>
<th>Acute Adverse Events (%)</th>
<th>Late Adverse Events (%)</th>
<th>Transvenous System (%)</th>
<th>Epicardial/Mixed System (%)</th>
<th>ICD Capability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital heart disease</td>
<td>13 (18%)</td>
<td>8 (11%)</td>
<td>26 (36%)</td>
<td>37/10 (51%/14%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>5 (31%)</td>
<td>1 (6%)</td>
<td>12 (75%)</td>
<td>4/0 (25%)</td>
<td>6 (37%)</td>
</tr>
<tr>
<td>Heart block</td>
<td>2 (14%)</td>
<td>1 (7%)</td>
<td>7 (50%)</td>
<td>7/0 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>p Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator.

**Figure 2.** (A) Chest film of a patient with an epicardial biventricular pacing system. (B) Chest film of a patient who required a mixed biventricular pacing system. The left ventricular lead was placed epicardially and tunneled to the generator, whereas the implantable cardioverter-defibrillator lead and atrial lead were placed transvenously.
However, the patients with prior pacemakers had a significantly longer QRS duration than those who did not (178 ± 31 ms vs. 160 ± 30.1 ms, p < 0.05), with greater improvement in QRS duration (46.2 ± 36.1 ms vs. 31.1 ± 22.9 ms, p < 0.05).

Univentricular hearts. Seven patients had single ventricle physiology. Three patients had completed a total cavopulmonary connection, whereas the other four had bidirectional Glenn shunts. These patients all received epicardial lead systems. Ventricular leads were placed as far apart as possible. Median age at implant was 3.1 years (5 months to 23.7 years). Ejection fraction was measured by radionuclide scan in four of the seven, whereas function was subjectively described in the remaining three. These patients had no significant increase in EF (7.3 ± 5.7 EF units) (p = 0.08) and no change in qualitative echo measurement, but did have a significant decrease in QRS duration of 44.8 ± 26.2 ms (p < 0.05). There was clinical improvement in two of the seven.

Systemic right ventricles. There were 17 patients with systemic right ventricles who received CRT therapy. Diagnoses included l-transposition of the great arteries in 13 and d-transposition of great arteries status after Senning or Mustard procedure in four. Median age at implant was 12.7 years (4.9 to 50.0 years). Ejection fraction data were available in 12 systemic right ventricle patients. These patients had a significant increase in systemic EF (13.3 ± 11.3 EF units) and a significant decrease in QRS duration (38.2 ± 29.4 ms) (p < 0.05). Thirteen of these patients had clinical improvement.

Non-responders. Non-responders were defined as those who had either no change in their EF with CRT, or a decrease in their EF. There were 11 non-responders. Table 4 compares baseline characteristics of responders with non-responders. Thirteen of these patients were receiving some anti-congestive medical therapy before upgrade (8 patients were receiving an angiotensin-converting enzyme inhibitor, 7 diuretics, and 3 beta-blockers). There was a significant difference in the EF before CRT, with the responders having a lower EF of 24.3 ± 11.0% versus an EF of 32.0 ± 14.2% in the non-responders (p = 0.04). QRS duration decreased an average of 33.4 ± 18.3 ms in non-responders (p < 0.05), which was not different than the responders (36.8 ± 24.7 ms).

Adverse events. Two patients had significant clinical deterioration closely following placement of biventricular pacemakers. One patient who was on oral anti-congestive agents required initiation of intravenous positive inotropic support after pacemaker placement, and one patient required extracorporeal membrane oxygenation after pacemaker placement. This patient subsequently died.

In the entire cohort, there were 23 acute adverse events reported in 20 patients, which are summarized in Table 5. These included three deaths. The deaths occurred four days and two weeks (two patients) after the procedure. There were five reported coronary sinus lead issues, including one instance where the coronary sinus could not be entered with the pacer lead secondary to small size (the patient was 20 years of age). There were three arrhythmic episodes, and three cases of inadequate defibrillation threshold in pacemakers with ICD capability (all three in transvenous systems). There were two device pocket hematomas, and one each of the following: pocket infection, cerebrovascular accident, bleeding, and perforation of the myocardium requiring surgical intervention.

Delayed adverse events occurred in 10 patients. These included two additional deaths. There were also three reports of coronary sinus lead dislodgement, one lead adaptor malfunction, one pacer site infection, and three arrhythmic episodes.

Thus, there was an overall adverse event rate of 29%. Overall mortality was 5%. Coronary sinus lead issues, which accounted for 23% of the reported complications, and were found in 18% of all transvenous pacemakers placed, were the single most common major complication.
Table 5. Acute and Late Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Acute</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>CVA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Site infection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Site hematoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate DFTs</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CS issues</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Dislodgement</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Difficulty placing lead</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Diaphragm capture</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Blood loss</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Atrial arrhythmia (flutter or fibrillation)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ventricular arrhythmia (including VT/VF)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>RA or RV lead issues</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cardiac perforation</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

CS = coronary sinus; CVA = cerebrovascular accident; DFTs = defibrillation threshold; RA = right atrial; RV = right ventricular; VF = ventricular fibrillation; VT = ventricular tachycardia.

No differences in complication rates could be seen when comparing transvenous placement versus epicardial or mixed placement of devices: acute adverse events were seen in 10 of 45 (22%) transvenous systems and 10 of 58 (17%) epicardial/mixed systems, whereas late events were found in 7 (15%) transvenous systems and 3 (5%) epicardial/mixed systems (p = NS for all). Arrhythmic episodes were found in four epicardial systems and two transvenous systems (p = NS). When comparing ICD systems versus pacing systems, there were also no significant differences in complication rates, with an acute adverse event rate of 37% versus 16% (p = 0.08) and a late adverse event rate of 11% versus 10% (p = NS). However, the small numbers of patients for comparison limit the power of this observation.

Deaths. EARLY DEATHS. One patient died suddenly four days after CRT implantation. This patient had aortic stenosis requiring an aortic valve replacement. He developed progressive left ventricular dysfunction and had an EF of 17% at the time of CRT therapy. The patient also had syncope but no documented arrhythmia. Four days after implantation of a biventricular pacemaker/ICD, he had a ventricular fibrillation cardiac arrest while climbing stairs. Interrogation of his device revealed appropriate therapy and conversion to normal sinus rhythm. He subsequently developed electrical storm that did not respond to any antiarrhythmics. He was emergently placed on extracorporeal membrane oxygenation support that was unsuccessful.

Two patients died within 30 days after their procedure. Neither patient had documented arrhythmia before CRT therapy. The first was a seven-year-old, status post–atrial septal defect closure, with surgical heart block in the first year of life. At age 7, he developed dilated cardiomyopathy (EF = 23%) and his dual-chamber pacemaker was upgraded to a biventricular system. Two weeks after implant, he presented to an emergency room in a wide complex tachycardia after a sudden collapse. After multiple defibrillation attempts, he was unable to be resuscitated. The second patient was a 39-year-old with left transposition of the great arteries, ventricular septal defect with complete atrioventricular block. He underwent biventricular pacemaker upgrade at the time of his double switch procedure. Unfortunately, he was not able to be weaned from cardiopulmonary bypass and was thus placed directly onto extracorporeal membrane oxygenation support. He died of pump failure two weeks after implant.

LATE DEATHS. There were two late deaths. Neither of these patients had prior documented arrhythmias. One of these occurred in a patient who had a ventricular septal defect repaired in infancy and developed surgical heart block requiring a VVIR pacemaker. At age 10, he was noted to have a severe cardiomyopathy with a shortening fraction of 10% despite optimal anticongestive therapy. He was upgraded to a biventricular pacemaker. He died suddenly eight weeks later. Interrogation of his device revealed runs of ventricular tachycardia.

The second late death occurred in a 35-year-old patient status post repair of atrioventricular septal defect who had progressive left ventricular dysfunction and required a ventricular assist device several months after CRT therapy was instituted. This patient died of incessant ventricular arrhythmias and poor cardiac output while on the ventricular assist device.

Study limitations. This study, while the largest experience in the pediatric population for this new therapy, is retrospective in nature, and thus has some limitations inherent to its design. The NYHA/Ross classification is highly subjective, especially when assigned in a retrospective manner. The varied cardiac anatomy in this study required multiple techniques for measuring EF, which can be difficult to compare.

DISCUSSION

Cardiac resynchronization therapy has been shown to be a powerful tool in the adult patient with left-sided heart failure. This therapy has been well tested in the adult patient with intraventricular conduction delay and ventricular dysfunction (1–3,5,7,17). However, there have been no equivalent studies of CRT performed in pediatric patients. Of note, there are comparatively few pediatric patients who fit the classic criteria employed for adults. Indeed, in this study, only 16% of patients had a biventricular pacing system implanted for cardiomyopathy, whereas 54% of patients fulfilled EF and QRS criteria for CRT in adults. The great majority of patients had poor systolic function and CHD, including patients with single ventricle physiology. Thus, indications for CRT are markedly different, with 71% of patients having CHD. The literature provides little guidance to predict the response to CRT of patients such as these. As such patients commonly develop congestive heart failure in early adulthood, and often become transplant candidates, a careful consideration of the effects of CRT in this unique group is essential.
Interestingly, though the indications for CRT were quite heterogeneous, patients overall showed an improvement in EF as well as clinical status. Furthermore, five of the six critically ill patients dependent upon positive inotropic support were weaned to oral therapy with the aid of biventricular pacing. No differences in response could be found based on the indication for implantation.

There were 11 patients whose EFs did not improve with CRT. These patients had a significantly better EF at baseline than the responders, raising the question of whether these patients were “too well” to benefit from CRT. Interestingly, three of these patients had improved clinical status despite having no change in their EF. Yu et al. performed a multivariate analysis of adult heart failure patients with CRT therapy and found that systolic dyssynchrony measured with tissue Doppler imaging was the only predictor of left ventricular remodeling (18). It is clear that QRS duration alone cannot determine which patients will improve, and that further work looking at the mechanical–electrical interaction is necessary in this population.

Almost one-half the patients who had CRT instituted in the present study had a previous pacemaker system in place. As might be expected, these patients’ QRS durations were somewhat more prolonged, and shortened more than patients who were not paced. These patients had the same improvement in EF and clinical status as did the patients who had intrinsic conduction delay. Thus it does not appear that the benefit of CRT in pediatric patients is dependent on intrinsic conduction delay per se. Further studies are needed to assess whether this therapy should be considered as a primary therapy when pacing is required.

Another group unique to this series is that of univentricular hearts. There were seven patients in whom multisite, univentricular pacing was attempted. These patients did not have a clinically significant change in EF with the institution of multisite pacing. Although the number of patients in this group is quite small, a few preliminary conclusions can be made. The effect of pacing on ventricular function was quite marginal in this group, all of whom required epicardial pacing. Therefore, the risk–benefit ratio in this group is less clearly in favor of pacing. This finding seems to contradict acute data reported by Zimmerman et al. (19) which found a 14% increase in cardiac output in single ventricle patients with multi-site pacing in the postoperative period.

Cardiac resynchronization therapy was instituted in 17 patients with systemic right ventricles. Janousek et al. (15) first reported on the use of CRT for systemic right ventricular failure in this subset of patients. We found that these patients had improvement in both systemic EF and clinical status with the institution of CRT.

We found marked variability in implantation technique, with half of the devices implanted using an epicardial or mixed approach, which is uncommon in the adult experience. This stresses the need for further development of new tools and techniques for accessing the posterior epicardial surface in the pediatric and CHD populations.

The high adverse event rate of 29% appears comparable to the experience with adults (20). Coronary sinus lead issues were found in 18% of patients who received transvenous systems, which is somewhat higher than what was found in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial (12% for dissection, perforation, or lead dislodgement) (17). This may be related to anatomic issues found in the pediatric patient or patient with CHD. As this is a relatively new technique, operator experience may also have a role in this issue.

There were five deaths reported in this series, comparable to the 5% mortality reported in the MIRACLE trial (17). Three of the five deaths were related to ventricular arrhythmias, whereas two appeared to be pump failure. The Comparison of Medical Therapy Pacing and Defibrillation in Heart Failure (COMPANION) trial showed a significant decrease (36%) in mortality with CRT/ICD therapy (1). Several other studies have suggested that CRT may actually suppress the incidence of ventricular arrhythmias (21,22). However, there have been other investigators who propose that multisite pacing may actually be proarrhythmic (23). We found several patients (including three of the five patients who died) who had new-onset ventricular arrhythmias after CRT therapy. Conversely, only 19% of our patients underwent CRT/ICD therapy, a much smaller percentage than that seen in recent adult trials. Whether the new-onset ventricular arrhythmia seen in this population represents true proarrhythmia or is simply a sequela of a severely ill population will need to be further investigated and may alter present indications for ICD placement.

Thus, while the indications for biventricular pacer placement differ markedly from the pediatric population to the adult population, there are pronounced hemodynamic benefits in both groups, as well as favorable electrical and mechanical changes in the heart. Further studies into the mechanism of this improvement in this vastly different substrate are needed, as are longer-term clinical studies.

**REFERENCES**


