CHAPTER 2
Right ventricular imaging: echocardiography

2.1
Review: cardiac resynchronization therapy in pediatric and congenital heart disease patients

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ABSTRACT

The number of patients with congenital heart disease (CHD) has significantly increased over the last decades. The CHD population has a high prevalence of heart failure during late follow-up and this is a major cause of mortality. Cardiac resynchronization therapy (CRT) may be a promising therapy to improve the clinical outcome of CHD and pediatric patients with heart failure. However, the CHD and pediatric population is a highly heterogeneous group with different anatomical substrates that may influence the effects of CRT. Echocardiography is the mainstay imaging modality to evaluate CHD and pediatric patients with heart failure and novel echocardiographic tools permit a comprehensive assessment of cardiac dyssynchrony that may help selecting candidates for CRT. This article reviews the role of CRT in the CHD and pediatric population with heart failure. The current inclusion criteria for CRT as well as the outcomes of different anatomical subgroups are evaluated. Finally, echocardiographic assessment of mechanical dyssynchrony in the CHD and pediatric population and its role in predicting response to CRT is comprehensively discussed.

INTRODUCTION

Heart failure is a major health burden with an estimated overall prevalence of 2-3% (1). Cardiac resynchronization therapy (CRT) has improved the clinical outcome of drug refractory heart failure in patients with poor left ventricular ejection fraction (LVEF) and wide QRS complex. CRT improves LV function by inducing a more synchronous contraction. Consequently, CRT has resulted in improvements in heart failure symptoms (New York Heart Association (NYHA) functional class, exercise capacity or quality of life) and all-cause mortality of heart failure patients (2-7). Currently, CRT is a class I indication for patients with NYHA functional class III or IV despite optimized pharmacological therapy, LVEF <35% and QRS duration >120 ms (8,9).

Advances in cardiac surgery have led to an increased survival of patients with congenital heart disease (CHD). As a result, the prevalence of CHD in the pediatric population has doubled over the last decades (10). Progressive heart failure is a major cause of death during late follow-up of patients with complex CHD (11,12). The excellent outcomes obtained with CRT in adult patients have raised interest to apply this therapy in CHD and pediatric patients with heart failure. However, the current inclusion criteria for CRT in adult populations may not be directly applied to pediatric patients. Etiologies of heart failure differ substantially between adults and children, with CHD as the mainstay cause in the pediatric population (13). In addition, within the CHD population there are several subgroups of patients according to (post-surgical) cardiac anatomy, including patients with a systemic LV, patients with a systemic right ventricle (RV) and patients with a single ventricle. These different groups may show different responses to CRT (14-16). Therefore, a detailed evaluation prior to CRT implantation may be crucial to identify those who will benefit from this therapy within this heterogeneous group of patients.

Cardiac imaging plays a central role in the evaluation of CHD and pediatric patients before CRT device implantation. Accurate assessment of ventricular volumes and function is mandatory before CRT implantation to assess heart failure severity and to accurately follow-up ventricular function. In addition, assessment of cardiac anatomy is crucial to anticipate the ventricular pacing lead implantation approach (epicardial or transvenous). Furthermore, the study of ventricular mechanical dyssynchrony and identification of the latest activated areas may help to define the most suited position of the ventricular pacing lead and may provide meaningful insight into the effects of CRT in the CHD and pediatric population. Several echocardiographic methods have been proposed to evaluate ventricular mechanical dyssynchrony (17). The assessment of ventricular dyssynchrony in the adult population has been demonstrated useful to identify patients who will benefit from CRT, with subsequently a better clinical outcome (17). However, the role of established dyssynchrony parameters based on tissue Doppler imaging (TDI), 2-dimensional (2D) speckle tracking and real-time 3-dimensional (RT3D) echocardiography to evaluate mechanical dyssynchrony has not been extensively studied in the CHD and pediatric population. This article reviews the role of CRT in chronic heart failure in the CHD and pediatric population, focusing particularly on the current inclusion criteria and outcomes of different anatomical subgroups. Finally, the different imaging
modalities to assess cardiac mechanical dyssynchrony in the CHD and pediatric population and their role in predicting response to CRT will be discussed.

EXPERIENCE OF CRT IN CHD AND PEDIATRIC PATIENTS

The main CRT trials on CHD and pediatric patients have included highly heterogeneous populations. According to an anatomical classification, different subgroups can be defined, including patients with:
- systemic LV failure,
- systemic RV failure,
- failure of the single ventricle.

The group of patients with **systemic LV failure** (Figure 1, panel A) consists of both pediatric patients with normal cardiac anatomy with heart failure due to cardiomyopathies or congenital atrioventricular block, and of patients (children and adults) with LV failure due to underlying CHD. Although the majority of evidence is based on case reports and small case series, several retrospective non-randomized trials including heterogeneous populations have reported favourable outcomes after CRT in this subgroup of patients. (14-16)

**Failure of the systemic right ventricle** (Figure 1, panel B) is commonly observed in patients with complete transposition of the great arteries who underwent atrial switch operation (Mustard or Senning procedure), and patients with congenital corrected transposition of the great arteries (double discordance). (26-28) A recent study evaluated the effects of CRT in eight patients with systemic RV failure. After a median follow-up of 17 months, RV ejection fraction significantly increased (mean change +10%, p=0.004) along with a decrease in QRS duration (from 161 ± 21 ms to 116 ± 22 ms, p<0.01). (29) Subsequent small studies further demonstrated favourable clinical outcomes in RV systemic failure patients treated with CRT, yielding improvements in NYHA functional class, RV ejection fraction and exercise performance. (14-16,21,30-33)

Finally, patients with **failure of the single ventricle** (Figure 1, panel C) may constitute the most challenging population. According to current surgical practice, most patients with one hypoplastic ventricle undergo surgical palliation by a Fontan procedure or total cavo-pulmonary connection. The systemic and pulmonary circulations are separated without interposition of a sub-pulmonary connection. The systemic ventricle supports the pulmonary circulation, while both caval veins are redirected to the pulmonary artery. The ventricle supporting the systemic circulation may be either of RV or LV morphology. Despite surgical intervention, heart failure is common in this subgroup of patients. (28) Bacha and colleagues studied the effects of CRT in 26 single-ventricle patients. (34) Multisite epicardial pacing with maximal distance between the wires yielded a significant reduction of QRS duration (from 94 ± 18 ms to 72 ± 11 ms, p<0.01) and a significant improvement in cardiac function.

The different anatomical classification of CHD patients may account for differences in response rates to CRT. In addition, cardiac anatomy may challenge lead implantation. In contrast to adult patients with heart failure, a surgical epicardial approach is commonly needed. Particularly, surgical

### Table 1. Retrospective cohorts on CRT in CHD and pediatric patients

<table>
<thead>
<tr>
<th>CRT studies in CHD and pediatric populations</th>
<th>Dubin et al.(15)</th>
<th>Cecchin et al.(14)</th>
<th>Janousek et al.(16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>103</td>
<td>60</td>
<td>109</td>
</tr>
<tr>
<td>Age range (y)</td>
<td>0.3 – 55</td>
<td>0.4 – 43</td>
<td>0.2 – 74</td>
</tr>
<tr>
<td>median</td>
<td>13</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>4.8 ± 4</td>
<td>range: 1 – 64</td>
<td>range: n/a</td>
</tr>
<tr>
<td>Before CRT</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NYHA functional class n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (14)</td>
<td>16 (27)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>49 (48)</td>
<td>25 (42)</td>
<td>median: 2.5</td>
</tr>
<tr>
<td>III-IV</td>
<td>39 (38)</td>
<td>19 (32)</td>
<td></td>
</tr>
<tr>
<td>Systemic ventricle EF (%)</td>
<td>26 ± 12</td>
<td>range: 8 – 70</td>
<td>range: n/a</td>
</tr>
<tr>
<td>Systemic ventricle EF improvement</td>
<td>median: 8.4</td>
<td>median: 36</td>
<td>median: 7.5</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>166 ± 33</td>
<td>range: 95 – 210</td>
<td>range: n/a</td>
</tr>
<tr>
<td>QRS (ms) improvement</td>
<td>median: 149</td>
<td>median: 36</td>
<td>median: 160</td>
</tr>
<tr>
<td>Successful implantations n (%)</td>
<td>n/a</td>
<td>49 (82)</td>
<td>93 (85)</td>
</tr>
<tr>
<td>Complications n (%)</td>
<td>20** (19)</td>
<td>71 (12)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>After CRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA functional class n (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>median change: -1.5</td>
</tr>
<tr>
<td>Systemic ventricle EF (%)</td>
<td>40 ± 15*</td>
<td>range: n/a</td>
<td>median change: +1.2</td>
</tr>
<tr>
<td>Systemic ventricle EF or NYHA improvement n (%)</td>
<td>126 ± 24*</td>
<td>range: n/a</td>
<td>range: n/a</td>
</tr>
<tr>
<td>Systemic ventricle EF improvement</td>
<td>median: 120*</td>
<td>median: 43*</td>
<td>median: 130*</td>
</tr>
<tr>
<td>Survival rate n (%)</td>
<td>98 (95)</td>
<td>65 (92)</td>
<td>102 (94)</td>
</tr>
</tbody>
</table>

Data of three retrospective CRT studies in CHD and pediatric populations. Continuous data are expressed in means ± standard deviation unless otherwise specified. Response rates are on an intention to treat basis, i.e. including the total amount of patients enrolled in the study, regardless of deaths, follow-up and unsuccessful implantations. Complications included: pocket hematomas, infection, lead issues, blood loss, ventricular arrhythmia, pneumothorax, pleural effusion, pulmonary edema, cardiac perforation, cardiovascular incidents and pacing threshold problems. Abbreviations: deaths: any deaths during follow-up period. EF: ejection fraction, mo: months, n/a: not available. NYHA: New York Heart Association functional class. Successful implantation: all patients alive and receiving CRT at latest follow-up date. * statistical difference (p<0.05) as compared with data before CRT implantation. ** majority of outcome data obtained at 3 months follow-up I includes early complications (<30 days after CRT implantation).
Table 2. Response rates of retrospective cohorts on CRT in CHD and pediatric patients, according to anatomical subgroups

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Systemic LV n (%)</td>
<td>79 (77)</td>
<td>38 (63)</td>
<td>62 (67)</td>
</tr>
<tr>
<td>Increase LVEF (%)</td>
<td>n/a</td>
<td>median: 8*</td>
<td>median: 13*</td>
</tr>
<tr>
<td>Decrease LVES (%)</td>
<td>n/a</td>
<td>median: 33*</td>
<td>median: 40*</td>
</tr>
<tr>
<td>Response rate defined as increase</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>LVES (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>NYHA improvement ≥ 1 class n (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>LVEF increase or NYHA improvement n (%)</td>
<td>n/a</td>
<td>17 (16)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Systemic RV n (%)</td>
<td>17 (16)</td>
<td>9 (15)</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Increase RVEF (%)</td>
<td>13 ± 11*</td>
<td>median: 14</td>
<td>7*</td>
</tr>
<tr>
<td>Decrease RVEF (%)</td>
<td>38 ± 29*</td>
<td>median: 15</td>
<td>median: 21</td>
</tr>
<tr>
<td>Response rate defined as increase</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>NYHA improvement ≥ 1 class n (%)</td>
<td>13 (76)</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>RVEF increase or NYHA improvement n (%)</td>
<td>n/a</td>
<td>2 (22)</td>
<td>19 (70)</td>
</tr>
<tr>
<td>Single ventricle n (%)</td>
<td>7 (7)</td>
<td>13 (22)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Increase LVEF or RVEF (%)</td>
<td>7.3 ± 5.7</td>
<td>median: 10</td>
<td>n/a</td>
</tr>
<tr>
<td>Decrease QRS (ms)</td>
<td>45 ± 26*</td>
<td>median: 13</td>
<td>n/a</td>
</tr>
<tr>
<td>Response rate defined as LVEF or RVEF</td>
<td>n/a</td>
<td>10 (77)</td>
<td>n/a</td>
</tr>
<tr>
<td>increase n (%)</td>
<td>n/a</td>
<td>2 (30)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>NYHA improvement ≥ 1 class n (%)</td>
<td>2 (30)</td>
<td>7 (54)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>RVEF/LVEF increase or NYHA improvement n (%)</td>
<td>n/a</td>
<td>3 (75)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Response rates after CRT in three retrospective studies in CHD and pediatric populations, displayed for every anatomical subgroup. Response percentages are on an intention to treat basis, i.e. including the total amount of patients enrolled in the study, regardless of deaths, follow-up and unsuccessful implantations.

Abbreviations: LVEF: left ventricular ejection fraction, NYHA: New York Heart Association class, RVEF: right ventricular ejection fraction.

* statistical difference (p<0.05) as compared with data before CRT implantation /patients with concurrent cardiac surgical procedure excluded

OUTCOME OF CRT IN CHD AND PEDIATRIC PATIENTS

Beyond case reports and small case series, data on mid and long-term outcome, as well as survival and complication rates of CRT in pediatric patients are limited to three retrospective studies including patients with all anatomical substrates and etiologies (Table 1).

First, Dubin et al. described the outcomes of 103 CHD and pediatric patients in a multicenter study. (15) After a mean duration of 4.8 months follow-up, a reduction in QRS duration (from 166 ± 33 ms to 126 ± 24 ms, p<0.01) and an increase in ejection fraction of the systemic ventricle (from 26 ± 12% to 40 ± 15%, p<0.05) were observed after CRT. Finally, the survival rate in this cohort was 95%.

Second, Cecchin and colleagues reported mid-term outcomes of 60 CHD and pediatric patients treated with CRT. (14) Significant improvement in the ejection fraction of the systemic ventricle (from 36% to 43%, p<0.01) and decrease in QRS duration (from 149 ms to 120 ms, p<0.01) were reported. A total of 65 (92%) patients survived during follow-up.

Third, Janousek and co-workers performed a multicenter trial on CRT including 109 CHD and pediatric patients. (16) Similar to the other series, a significant improvement in ejection fraction of the systemic ventricle (from 36% to 43%, p<0.01) and decrease in QRS duration (from 149 ms to 120 ms, p<0.01) were reported. Finally, 94% of patients survived during follow-up.

In these three studies, response rates (based on intention to treat) ranged between 32% and 76%, depending on the established end points. Dubin and colleagues reported a response rate of 76%, defined as an improvement in ejection fraction of the systemic ventricle (15) In the study by Cecchin and co-workers, 32% of patients exhibited an improvement in NYHA functional class, and 65% of patients improved in either NYHA functional class or ejection fraction of the systemic ventricle. (14) Finally, Janousek et al. defined response as improvement in NYHA functional class or ejection fraction of the systemic ventricle and reported a response rate of 72% (16).

The different anatomical subgroups may account for differences in the response rates to CRT.
Response rates of the anatomical subgroups are depicted in Table 2. The majority of patients had a systemic LV (63% to 77%). Janousek et al. reported a response rate of 69% in this subgroup, defined by an increase in either LVEF or NYHA functional class.[16]

The subgroup of patients with a systemic RV made up 15% to 29% of the cohorts (Table 3). Dubin and colleagues reported an improvement in NYHA functional class in 76% of this subgroup.[15] In addition, defining response rate by RV ejection fraction or NYHA functional class improvement, the trial by Cecchin et al. reported a response rate of 22%,[14] whereas Janousek and co-workers observed improvement in 70% of patients with a systemic RV.[16]

Single ventricle patients constituted 4% to 22% of the cohorts (Table 3). Improvement in NYHA functional class was observed in 30% to 54% of these patients.[14-16] In addition, Janousek et al. observed an echocardiographic or clinical response in 75% of the patients of this subgroup.[16]

Finally, 55 to 77% of patients in the three studies on CRT had a pacemaker before up-grading to

**Figure 1. Anatomical subgroups of CHD and pediatric patients**

**Panel A:** Example of a CHD patient with a systemic left ventricle. Apical 4-chamber view of a patient after correction of tetralogy of Fallot. The left ventricle is the systemic ventricle in patients with tetralogy of Fallot. The right ventricle is dilated in this patient due to pulmonary regurgitation and subsequent chronic volume overload. In tetralogy of Fallot, systemic left ventricular failure may occur during late follow-up. **Panel B:** Example of a CHD patient with a systemic right ventricle. Apical 4-chamber view of a patient with congenital corrected transposition of the great arteries. The (morphological) right ventricle is the systemic ventricle in patients with congenital corrected transposition of the great arteries. Note the trabecularization of the systemic right ventricle and the (more apical) septal insertion of the atrioventricular valve compared with the (morphological) left ventricle. Systemic right ventricular failure is a common problem in patients with congenital corrected transposition of the great arteries. **Panel C:** Example of a CHD patient with a single ventricle. Apical “4-chamber” view of a patient with hypoplastic left ventricle. The single ventricle is of right ventricular morphology. Note the very hypoplastic left ventricle. Failure of the single ventricle is common in patients with a hypoplastic left ventricle. Abbreviations: syst L V: systemic left ventricle, syst RV: systemic right ventricle, V: ventricle.

**Figure 2. Atrioventricular dyssynchrony**

Example of a pediatric patient with idiopathic dilated cardiomyopathy and atrioventricular dyssynchrony as assessed with pulsed wave Doppler echocardiography. Left ventricular filling time is reduced (<40% of RR interval) and the early (E-wave) and late (A-wave) diastolic inflow waves are fused.Abbreviation: LV: left ventricle

**Figure 3. Inter-ventricular dyssynchrony**

Example of inter-ventricular dyssynchrony in a patient with congenital atrioventricular block and chronic right ventricular pacing. Inter-ventricular dyssynchrony can be evaluated with pulsed wave Doppler echocardiography. The time from onset of the QRS complex to the onset of flow (pre-ejection interval) is measured in the pulmonary artery and in the left ventricular outflow tract. The difference between both pre-ejection times yields the so-called inter-ventricular mechanical delay (IVMD). In this example, the IVMD is 45 ms (>40 ms).[6] Abbreviations: Ao: aorta, Pulm: pulmonary artery.
In the study of Janousek and colleagues, the patients with failure of the systemic LV who were upgraded from single-site pacing to biventricular pacing showed the highest response rate. In addition, these patients showed a significantly larger improvement in NYHA functional class and a larger extent of LV reverse remodeling as compared with the rest of the study population.

Based on this clinical evidence, CRT may be a promising therapy to improve cardiac performance and clinical outcome of CHD and pediatric patients with heart failure. However, several issues need further investigation. First, the median follow-up duration of the three trials described is limited (4.8 to 8.4 months) (Table 1). Additional trials reporting on the long-term effects of CRT in CHD and pediatric patients are warranted. Furthermore, comparisons of the CRT response rate between heart failure adult patients and CHD and pediatric patients should take into consideration patient age and size related differences. Finally, current selection criteria remain controversial in CHD and pediatric patients, and accurate selection of patient subgroups that will benefit from CRT is warranted.

SELECTION OF CHD AND PEDIATRIC PATIENTS FOR CRT

Current inclusion criteria for CRT in the adult populations are: NYHA functional class III or IV despite optimal pharmacological therapy, LVEF <35% and QRS duration >120 ms. However, the majority of the studies on CRT in CHD and pediatric populations have not applied these criteria prospectively.

NYHA functional class III or IV despite optimal pharmacological therapy is one of the inclusion criteria. In CRT trials enrolling CHD and pediatric populations, the majority of patients were in NYHA functional class I or II, indicating only mild heart failure. This discrepancy with the current guidelines likely resulted from a substantial proportion of CHD and pediatric patients with a concomitant indication for cardiac surgery (15% to 32%), ICD implantation or anti-bradycardia pacing (55-77%). These concomitant indications may well have accelerated decision-making on CRT implantation during the same procedure in patients with only mild heart failure. In addition, Janousek et al. demonstrated that NYHA functional class is a strong determinant of CRT response in CHD and pediatric patients, with a higher favourable response rate in those patients with NYHA functional class I-II than in patients in NYHA functional class III-IV. Indeed, the benefits of CRT in adult patients with mild symptomatic heart failure have been evaluated. The REsynchronization reVERSes Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial included over 600 heart failure patients in NYHA functional class I-II undergoing CRT implantation. After 1 year follow-up, reverse LV remodeling and improved LVEF was observed, indicating a beneficial effect of CRT even with mild clinical heart failure. Therefore, the implantation of CRT at an early stage may help to prevent the progression and/or the development of heart failure. However, when CRT is considered in asymptomatic or mildly symptomatic patients, the possible effects of implantation of a device on quality of life need to be weighed against the benefits of CRT on cardiac performance. Importantly, in young pediatric patients, grading of heart failure by NYHA class may not be reliable. In those patients, careful monitoring of ventricular performance by measuring ejection fraction may yield more reliable data about response to CRT.

Another inclusion criterion is LVEF <35%. The mean value of systemic ventricular ejection fraction in the three CHD and pediatric cohorts varied between 26% and 36%. Dubin et al. observed a lower baseline ejection fraction of the systemic ventricle in non responders (24 ± 11% versus 32 ± 14%, p=0.04). However, evaluation of this parameter in the CHD and pediatric population is hampered by methodological difficulties. Although echocardiographic LVEF is reliable in patients with a systemic LV in patients with RV failure (systemic RV or single RV), standard echocardiography is less accurate for quantifying RV volumes and ejection fraction due to the complex RV geometry. In this regard, quantification with magnetic resonance imaging is currently preferred.

Figure 4. Left ventricular dyssynchrony: M-mode septal-to-posterior wall motion delay

Example of left ventricular dyssynchrony in a patient with a truncus arteriosus after aortic and pulmonary valve replacement. The patient shows flattening of the septum in the parasternal short axis view due to right ventricular outflow obstruction. Left ventricular dyssynchrony is measured with M-mode septal-to-posterior wall motion delay (SPWMD). From the parasternal short-axis M-mode recording of the left ventricle, a delay of 240 ms is observed between the peak systolic inward motion of the septum and the peak systolic inward motion of the posterior wall. (SPWMD ≥ 130 ms indicates left ventricular dyssynchrony). Abbreviations: SPWMD, septal-to-posterior wall motion delay.
As mentioned before, prolonged QRS duration is the only criterion considered by current guidelines for cardiac dyssynchrony. However, it has been shown that the relationship between electrical conduction delay and mechanical dyssynchrony is not straightforward. In addition, the value of QRS complex duration to predict response to CRT may be suboptimal with a sensitivity and specificity of 54%. The mean QRS duration in the three retrospective CHD and pediatric cohorts described above was >120 ms. However, Dubin et al. stated that only 54% of included patients met the combined criteria of QRS >120 ms and systemic ventricular ejection fraction <35%. In addition, Pham et al. evaluated the effects of biventricular pacing in 19 CHD patients with a narrow QRS complex (96 ± 18 ms). Temporary epicardial leads were implanted and several pacing modes, including biventricular pacing, were tested for 10 minutes each. Compared to conventional pacing modalities, biventricular pacing was associated with significant improvements in cardiac index in these patients with narrow QRS complex. Furthermore, various imaging studies in pediatric patients with dilated cardiomyopathy have demonstrated the presence of LV mechanical dyssynchrony despite narrow QRS complex. These findings indicate that pediatric patients may benefit from CRT, even in the presence of a narrow QRS complex. Indeed, several adult trials included heart failure patients with narrow QRS complex and LV mechanical dyssynchrony, and observed favourable outcomes after CRT.

As mentioned above, important differences with the current CRT inclusion criteria are observed in the pediatric cohorts, especially with regard to clinical heart failure classification and QRS duration. Moreover, the anatomical substrate may constitute an additional issue to be considered before CRT implantation in these populations. Cardiac imaging of ventricular function and mechanics (dyssynchrony) may provide additional insight into the effects of CRT and improve selection of CHD and pediatric patients who will benefit from CRT.

**ECHOCARDIOGRAPHIC ASSESSMENT OF DYSSYNCHRONY**

As mentioned before, prolonged QRS duration is the only criterion considered by current guidelines for cardiac dyssynchrony. However, QRS duration might not be accurate enough to identify those patients who will benefit from CRT. It has been demonstrated that the presence of mechanical dyssynchrony, rather than electrical dyssynchrony, may be a more robust parameter to select patients who will benefit from CRT. Mechanical dyssynchrony may occur at different levels (atrioventricular, inter-ventricular and intra-ventricular) and can be assessed with various cardiac imaging techniques. Echocardiography is the mainstay imaging modality to evaluate cardiac dyssynchrony and permits comprehensive assessment of these three different types of dyssynchrony.

**Atrioventricular dyssynchrony**

Atrioventricular dyssynchrony refers to a prolonged delay in atrioventricular sequential contraction, resulting from prolongation of the PR interval, QRS widening, or both. With the use of pulsed-wave Doppler echocardiography, atrioventricular dyssynchrony can be assessed by measuring LV filling time from transmural flow recordings. When the atrioventricular delay is prolonged, the early (E-wave) and late (A-wave) diastolic waves fuse and diastolic filling time of the ventricles is shortened. In adult patients, a LV filling time/RR interval >40% indicates atrioventricular dyssynchrony (Figure 2). In CHD and pediatric patients with LV systemic failure, no data on LV filling time are available so far. Nevertheless, surgical or congenital atrioventricular block may cause atrioventricular dyssynchrony and therefore the threshold of LV filling time/RR interval >40% needs investigation. However, in CHD patients with systemic RV failure, one small study provided data on RV filling time. Janousek et al. assessed RV filling time before and after CRT in eight patients with systemic RV failure and RBBB. RV filling time was calculated from the transthoracic pulsed-wave Doppler spectral signal. At 17 months follow-up, RV filling time (normalized for RR interval) had increased from 45.1 ± 6.5% to 50.0 ± 6.1% (p < 0.01).

**Inter-ventricular dyssynchrony**

Inter-ventricular dyssynchrony refers to contraction delay between the RV and the LV. Several indexes have been proposed to assess this type of cardiac dyssynchrony. One of the first was the inter-ventricular mechanical delay (IVMD) assessed with pulsed-wave Doppler echocardiography. IVMD is obtained by calculating the difference between aortic and pulmonary pre-ejection intervals (the time from the onset of QRS to the onset of flow) (Figure 3). Additionally, IVMD <40 ms indicates inter-ventricular dyssynchrony. The CARE-HF trial demonstrated the use of this index to predict response to CRT. Differences between CHD patients and adult heart failure patients may account for different IVMD cut-off values. For example, in patients with transposition of the great arteries (with normal LVEF), the aortic and pulmonary pre-ejection intervals differ from healthy individuals.

Intra-ventricular dyssynchrony: left ventricle

Intra-ventricular dyssynchrony of the LV (LV dyssynchrony) has shown to be an independent determinant of response to CRT and long-term survival in adults with heart failure. The assessment of LV dyssynchrony can be performed with various methods, evaluating time between mechanical events of two or more LV segments. Pitzalis et al. introduced the use of M-mode echocardiography to assess LV dyssynchrony. From the parasternal short-axis view of the LV, the time difference between the maximal systolic inward motion of the septal and posterior wall was...
calculated: the so-called septal-to-posterior wall motion delay (SPWMD) (Figure 4). A cut-off value of SPWMD of $\geq 130$ ms was proposed to predict response to CRT. In the CHD pediatric population several case reports and two small trials have used this index to evaluate the effects of CRT.\(^{(24;39;41;60;61)}\) For example, Tomaske and colleagues described six children with CHD and systemic LV failure who were treated with CRT.\(^{(24)}\) In these patients, SPWMD decreased from $312 \pm 24$ ms to $95 \pm 57$ ms ($p=0.03$) after one month follow-up, along with an improved LV EF (from $41 \pm 6\%$ to $53 \pm 8\%, p=0.03$) and a trend towards a decreased LV end-diastolic volume (from $70 \pm 22$ ml/m$^2$ to $63 \pm 18$ ml/m$^2$, $p=0.09$).

The advent of TDI, measuring regional myocardial velocities, has provided useful parameters to assess LV dyssynchrony, identifying responders to CRT with high specificity and sensitivity.\(^{(17)}\) Both pulsed-wave TDI and color-coded TDI can be used to assess LV dyssynchrony. Unlike pulsed-wave TDI, color-coded TDI can provide myocardial velocity tracings of two or more segments simultaneously (Figure 5). The feasibility and accuracy of color-coded TDI to evaluate LV dyssynchrony have been extensively explored in studies on CRT in the adult population.\(^{(17;62-64)}\) One of the first indices was the time difference between peak systolic velocity of the septal and lateral segments (septal-to-lateral wall motion delay) of $75$ ms in this patient ($>60$ ms)\(^{(62)}\). Abbreviations: SLWMD: septal-to-lateral wall motion delay. TDI: tissue Doppler imaging.
In pediatric populations, the usefulness of these indices has been demonstrated in several case reports and one small trial. Tomaske and co-workers applied a 4-segment TDI model in six CHD patients with systemic LV failure. At baseline, the maximum intra-LV delay between two basal and two mid-ventricular LV segments in the apical 4-chamber view was 64 ± 10 ms and improved to 37 ± 8 ms after one month of CRT (p=0.03), along with an improved LV systolic performance.

In addition to myocardial velocity, myocardial strain can be obtained from color-coded TDI images. The advantage of strain imaging over myocardial velocity imaging is that strain indicates active myocardial deformation or contraction whereas velocity represents passive motion or displacement. Differences in time to peak strain can be calculated to quantify LV dyssynchrony.

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Finally, the advent of novel echocardiographic techniques, including 2D strain and RT3DE has enabled assessment of dyssynchrony by evaluating active myocardial deformation (2D strain) or by evaluation of volumetric changes in a 3-dimensional fashion (RT3DE).

2D strain imaging or speckle-tracking strain imaging is a novel echocardiographic technique that permits multidirectional and angle-independent assessment of LV deformation. With this technique, the so-called speckles (natural acoustic markers equally distributed within the myocardium in 2D gray-scale images) are tracked frame-by-frame throughout the cardiac cycle. The change of their position relative to their original position is used to calculate myocardial strain. LV dyssynchrony can be characterized by evaluating radial strain (thickening of the myocardium in the short-axis views) (Figure 7). At the mid ventricular short-axis view of the LV, a maximum difference of ≥130 ms in time to peak strain between the antero-septal and the posterior LV segments has shown to predict favourable response to CRT in adult populations. Other adult series have evaluated the use of circumferential (LV shortening along the short-axis curvature of the LV) and longitudinal strain to measure LV dyssynchrony and to evaluate the effects of CRT.
and co-workers investigated LV dyssynchrony by assessing 2D circumferential strain in 6 CHD patients who underwent CRT for systemic LV failure. The maximum difference between the earliest and the latest activated segments and the standard deviation of time to peak strain of 12 segments were calculated at baseline and at one month follow-up. Both dyssynchrony parameters decreased significantly at one month follow-up after CRT (maximum difference decreased from 201 ± 35 ms to 99 ± 23 ms, p = 0.03; the standard deviation decreased from 72 ± 14 ms to 40 ± 15 ms, p = 0.03). Along with the mechanical resynchronization, the LVEF improved significantly at one month follow-up (from 41 ± 6% to 53 ± 8%, p = 0.03). In addition, 2D strain imaging permits evaluation of the latest activated areas where the LV pacing lead should ideally be placed. In adult populations, the position of the LV pacing lead concordant with the latest activated segment has demonstrated to be a determinant of positive response to CRT and superior long-term outcome. In CHD and pediatric studies, the usefulness of this technique to identify the latest activated segment and to guide the LV lead placement has been also demonstrated.

Finally, RT3DE provides regional time-volume curves for the evaluation of LV dyssynchrony (Figure 8). LV dyssynchrony is assessed by calculating the systolic dyssynchrony index (SDI). The standard deviation of time to minimum systolic volume of 16 LV segments is calculated. Marsan et al. demonstrated that a SDI cut-off value of 6.4% predicted long-term CRT response with high sensitivity (88%) and specificity (85%). Concerning CHD patients, Bacha et al. performed RT3DE in 10 single ventricle patients who received multisite pacing post-operatively. At 48 hours after CRT, the SDI of the single ventricle decreased significantly (from 10.3 ± 4.8 to 6.0 ± 1.4, p = 0.05).

The proposed inter-ventricular dyssynchrony parameters in the adult trials resemble the observations on LV dyssynchrony in pediatric and CHD patients. However, the predictive value of inter-ventricular dyssynchrony of the LV in CHD and pediatric patients may vary in the various anatomical subgroups. Furthermore, several factors such as previous pacing strategies, the presence and location of scar tissue and hemodynamic abnormalities may influence the CRT response. Additional trials are needed to establish cut-off values of LV dyssynchrony in CHD and pediatric patients, taking into consideration the various anatomical subgroups.

**Intra-ventricular dyssynchrony: right ventricle**

Similar to the assessment of intra-ventricular dyssynchrony of the LV in the adult population, intra-ventricular dyssynchrony of the RV has been studied in CHD patients with systemic RV failure. Van de Veire et al. assessed septal-to-lateral delay within the RV in the apical four-chamber view with color-coded TDI in a patient with RV-systemic failure who was upgraded from conventional pacing to CRT. After two weeks, the RV septal-to-lateral delay decreased from 80 ms to completely synchronous contraction and exercise capacity improved significantly. In addition, Janoušek et al. evaluated intra-ventricular dysynchrony of the RV with TDI derived strain before and after CRT in eight patients with RV systemic failure. RV dyssynchrony was quantified by measuring the largest delay in time to peak strain between four mid-ventricular RV segments (septal, lateral, anterior, posterior). After 4 days of CRT, RV dyssynchrony significantly reduced (from 138 ± 59 ms to 64 ± 21 ms, p = 0.042). In addition, RVEF, as assessed with radionuclide angiography at 4 months follow-up, improved from 41.5% to 45.5% (p = 0.01).

According to these data, assessment of intra-ventricular dyssynchrony of the RV could be useful in selecting patients with RV failure for CRT. However, unlike LV dyssynchrony assessment, characterization of RV dyssynchrony has been less explored, and additional studies evaluating RV dyssynchrony are needed to determine its value for predicting success of CRT in RV failure.

**CONCLUSION AND FUTURE PERSPECTIVE**

The beneficial effects of CRT on clinical outcomes and LV function of adult heart failure patients has encouraged the use of this therapy in other populations, such as CHD and pediatric patients. The population with CHD is growing, and this subgroup of patients has a high prevalence of heart failure during late follow-up. Although some studies have demonstrated the beneficial effects of CRT in CHD and pediatric patients, there are several concerns. First, the population of CHD and pediatric patients included in the studies is highly heterogeneous, comprising various anatomical substrates (systemic LV, systemic RV, single ventricle) and etiologies of heart failure (chronic single-site ventricular pacing). Furthermore, heterogeneity in this population results from patient age and size variations. Second, the current adult selection criteria may not be suitable for the CHD and pediatric heart failure population. Only a minority of CHD and pediatric patients included in studies on CRT fulfilled the adult guidelines of QRS >120 ms, NYHA functional class III or IV and LVEF <35%. The population with CHD is growing, and this subgroup of patients has a high prevalence of heart failure during late follow-up. Although some studies have demonstrated the beneficial effects of CRT in CHD and pediatric patients, there are several concerns. First, the population of CHD and pediatric patients included in the studies is highly heterogeneous, comprising various anatomical substrates (systemic LV, systemic RV, single ventricle) and etiologies of heart failure (chronic single-site ventricular pacing). Furthermore, heterogeneity in this population results from patient age and size variations. Second, the current adult selection criteria may not be suitable for the CHD and pediatric heart failure population. Only a minority of CHD and pediatric patients included in studies on CRT fulfilled the adult guidelines of QRS >120 ms, NYHA functional class III or IV and LVEF <35%.

C Third, the various anatomical substrates may result in patterns of cardiac dyssynchrony that may not be accurately characterized with ECG criteria. The study of mechanical dyssynchrony with various imaging modalities may provide a more accurate definition of cardiac dyssynchrony and improve selection of those CHD and pediatric patients who have the highest likelihood of response to CRT. However, the feasibility and performance of the various dyssynchrony parameters in CHD and pediatric patients may differ from those observed in adult heart failure patients.

In conclusion, CRT may be a promising therapy to improve the clinical outcome of CHD and pediatric patients with heart failure. However, more studies are needed to establish appropriate guidelines for patient selection, taking into account the different anatomical subgroups.
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