Cardiac resynchronization therapy in paediatric and congenital heart disease patients

Annelies E. van der Hulst, Victoria Delgado, Nico A. Blom, Nico R. van de Veire, Martin J. Schalij, Jeroen J. Bax, Arno A.W. Roest, and Eduard R. Holman

1Department of Paediatric Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and 2Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Received 19 October 2010; revised 14 January 2011; accepted 4 March 2011; online publish-ahead-of-print 30 March 2011

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 paediatric patients with heart failure. However, the CHD and paediatric 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 paediatric 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 paediatric 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 paediatric population and its role in predicting response to CRT is comprehensively discussed.

Keywords
Cardiac resynchronization therapy • Congenital heart disease • Echocardiography

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 paediatric 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 paediatric patients with heart failure. However, the current inclusion criteria for CRT in adult populations may not be directly applied to paediatric patients. Aetiologies of heart failure differ substantially between adults and children, with CHD as the mainstay cause in the paediatric 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 paediatric 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 paediatric population. Several echocardiographic methods have been proposed to evaluate ventricular mechanical dyssynchrony. The assessment of ventricular dyssynchrony in the adult populations has been demonstrated useful to identify patients who will benefit from CRT, with subsequently a better clinical outcome. However, the role of established dyssynchrony parameters based on tissue Doppler imaging (TDI), two-dimensional (2D) speckle tracking and real-time three-dimensional (RT3D) echocardiography to evaluate mechanical dyssynchrony has not been extensively studied in the CHD and paediatric population.

This article reviews the role of CRT in chronic heart failure in the CHD and paediatric 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 paediatric population and their role in predicting response to CRT will be discussed.

**Experience of cardiac resynchronization therapy in congenital heart disease and paediatric patients**

The main CRT trials on CHD and paediatric 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 1A) consists of both paediatric 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.

Failure of the systemic right ventricle (Figure 1B) 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). 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 to 116 ± 22 ms, *P* < 0.01). 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.

Finally, patients with failure of the single ventricle (Figure 1C) 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 ventricle, and 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. Bacha et al. studied the effects of post-operative CRT in 26 single-ventricle patients. Multisite epicardial pacing with maximal distance between the wires yielded a significant reduction of QRS duration (from 94 ± 18 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 epicardial lead implantation may be preferred in small patients or in patients with a concomitant cardiac surgical indication. However, the three largest trials including CHD and paediatric patients report no differences in complications during CRT implantation or in clinical outcome between the patients and paediatric patients report no differences in complications during CRT implantation or in clinical outcome between the patients with transvenous or epicardial lead implantation.14 – 16

Beyond the anatomical classification as described above, a substantial part of the studies on CRT in paediatric and CHD patients includes patients who previously underwent conventional single-site pacing for congenital or surgical atrioventricular block.14 – 16 In these patients, chronic single-site ventricular pacing may cause failure of the systemic ventricle at long-term follow-up.35 – 38 Several small series have reported promising results with significant clinical and echocardiographic improvement after CRT upgrading.21,24,25,30,32,33,39 – 41 For example, Moak et al. describe a series of six patients with LV failure after long-term single-site pacing. Along with clinical improvement in all patients, LVEF significantly increased (from 34 ± 6 to 60 ± 2%, P = 0.003) after upgrade to CRT.41

### Outcome of cardiac resynchronization therapy in congenital heart disease and paediatric 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

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Retrospective cohorts on cardiac resynchronization therapy in congenital heart disease and paediatric patients</th>
<th>CRT studies in CHD and paediatric populations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dubin et al.16</td>
<td>Cecchin et al.14</td>
</tr>
<tr>
<td>Number of patients (n)</td>
<td>103</td>
<td>60</td>
</tr>
<tr>
<td>Age range (y)</td>
<td>0.3 – 55</td>
<td>0.4 – 43</td>
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<tr>
<td>median</td>
<td>13</td>
<td>15</td>
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<tr>
<td>Follow-up (mo)</td>
<td>4.8 ± 4</td>
<td>Range: 1–64</td>
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<td></td>
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<td>Median: 8.4*</td>
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<td>Before CRT</td>
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<tr>
<td>NYHA functional class n (%)</td>
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<td></td>
</tr>
<tr>
<td>I</td>
<td>15 (14)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>II</td>
<td>49 (48)</td>
<td>25 (42)</td>
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<tr>
<td>II–IV</td>
<td>39 (38)</td>
<td>19 (32)</td>
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<tr>
<td>Systemic ventricle EF (%)</td>
<td>26 ± 12</td>
<td>Range: 8–70</td>
</tr>
<tr>
<td>QRS (ms)</td>
<td>166 ± 33</td>
<td>Median: 36</td>
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<td>Successful implantations n (%)</td>
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<tr>
<td>Complications n (%)</td>
<td>20² (19)</td>
<td>6 (10)</td>
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<tr>
<td>After CRT</td>
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<tr>
<td>NYHA functional class n (%)</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Systemic ventricle EF (%)</td>
<td>40 ± 15*</td>
<td>Range: n/a</td>
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<tr>
<td>QRS (ms)</td>
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<td>Range: n/a</td>
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<tr>
<td>Successful implantations n (%)</td>
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<td>49 (82)</td>
</tr>
<tr>
<td>Survival rate n (%)</td>
<td>98 (95)</td>
<td>65 (92)</td>
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</table>

Data of three retrospective CRT studies in CHD and paediatric 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 haematoma, infection, lead issues, blood loss, ventricular arrhythmia, pneumothorax, pleural effusion, pulmonary oedema, cardiac perforation, cardiovascular incidents and pacing threshold problems. 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; y, years.

²Statistical difference (P < 0.05) when compared with data before CRT implantation.

Majority of outcome data obtained at 3 months follow-up.

Includes early complications (<30 days after CRT implantation).
paediatric patients are limited to three retrospective studies including patients with all anatomical substrates and aetiology 

First, Dubin et al.\textsuperscript{15} described the outcomes of 103 CHD and paediatric patients in a multicenter study. After a mean duration of 4.8 months follow-up, a reduction in QRS duration (from 166 ± 33 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 et al.\textsuperscript{14} reported mid-term outcomes of 60 CHD and paediatric patients treated with CRT. Significant improvement in the ejection fraction of the systemic ventricle (from 36 to 43%, \( P < 0.01 \)) and decrease in QRS duration (from 149 to 120 ms, \( P < 0.01 \)) were reported. A total of 65 (92%) patients survived during follow-up.

Third, Janousek et al.\textsuperscript{16} performed a multicenter trial on CRT including 109 CHD and paediatric patients. Similar to the other series, a significant improvement in ejection fraction of the systemic ventricle (from 27 to 39%, \( P < 0.01 \)) and decrease in QRS duration (from 160 to 130 ms, \( P < 0.01 \)) were noted. 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 endpoints. Dubin et al.\textsuperscript{15} reported a response rate of 76%, defined as an improvement in ejection fraction of the systemic ventricle. In the study by Cecchin et al.\textsuperscript{14}, 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. Finally, Janousek et al.\textsuperscript{16} defined response as improvement in NYHA functional class or ejection fraction of the systemic ventricle and reported a response rate of 72%.

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 (63–77%). Janousek et al.\textsuperscript{16} reported a response rate of 69% in this subgroup, defined by an increase in either LVEF or NYHA functional class.

The subgroup of patients with a systemic RV made up 15–29% of the cohorts (Table 2). Dubin et al.\textsuperscript{15} reported an improvement in NYHA functional class in 76% of this subgroup. In addition, defining response rate by RV ejection fraction or NYHA functional class improvement, the trial by Cecchin et al.\textsuperscript{14} reported a response rate

| Table 2 | Response rates of retrospective cohorts on cardiac resynchronization therapy in congenital heart disease and paediatric patients, according to anatomical subgroups |
|---|---|---|---|
| **CRT studies in CHD and paediatric populations** | **Dubin et al.\textsuperscript{15}** | **Cecchin et al.\textsuperscript{14}** | **Janousek et al.\textsuperscript{16}** |
| **Systemic LV** | | | |
| n (%) | 79 (77) | 38 (63) | 62 (67) |
| Increase LVEF (%) | n/a | Median: 8\(^a\) | Median: 13\(^a\) |
| Decrease QRS (ms) | n/a | Median: 33\(^a\) | Median: 40\(^a\) |
| **Response rate defined as** | | | |
| Increase LVEF n (%) | n/a | n/a | n/a |
| NYHA improvement ≥ 1 class n (%) | n/a | n/a | n/a |
| LVEF increase or NYHA improvement n (%) | n/a | n/a | 43 (69) |
| **Systemic RV** | | | |
| n (%) | 17 (16) | 9 (15) | 27 (29) |
| Increase RVEF (%) | 13 ± 11\(^b\) | Median: 14 | 7\(^b\) |
| Decrease QRS (ms) | 38 ± 29\(^c\) | Median: 15 | Median: 21 |
| **Response rate defined as** | | | |
| Increase RVEF n (%) | n/a | n/a | n/a |
| NYHA improvement ≥ 1 class n (%) | 13 (76) | n/a | n/a |
| RVEF increase or NYHA improvement n (%) | n/a | 2 (22) | 19 (70) |
| **Single ventricle** | | | |
| n (%) | 7 (7) | 13 (22) | 4 (4) |
| Increase LVEF or RVEF (%) | 7.3 ± 5.7 | median: 10 | n/a |
| Decrease QRS (ms) | 45 ± 26\(^c\) | median: 13 | n/a |
| **Response rate defined as** | | | |
| LVEF or RVEF increase n (%) | n/a | 10 (77) | n/a |
| NYHA improvement ≥ 1 class n (%) | 2 (30) | 7 (54) | 2 (50) |
| RVEF/LVEF increase or NYHA improvement n (%) | n/a | n/a | 3 (75) |

Response rates after CRT in three retrospective studies in CHD and paediatric 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. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class; RVEF, right ventricular ejection fraction.

\(^a\)Statistical difference (\( P < 0.05 \)) when compared with data before CRT implantation.

\(^b\)Patients with concurrent cardiac surgical procedure excluded.
of 22%, whereas Janousek et al. observed improvement in 70% of patients with a systemic RV.

Single-ventricle patients constituted 4–22% of the cohorts (Table 2). Improvement in NYHA functional class was observed in 30–54% of these patients. In addition, Janousek et al. observed an echocardiographic or clinical response in 75% of the patients of this subgroup.

Finally, 55–77% of patients in the three studies on CRT had a pacemaker before up-grading to CRT. In the study of Janousek et al., 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 remodelling when compared with the rest of the study population.

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

Selection of congenital heart disease and paediatric patients for cardiac resynchronization therapy

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 paediatric 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 paediatric 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 paediatric patients with a concomitant indication for cardiac surgery (15–32%), 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 paediatric 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 remodelling 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 paediatric 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 paediatric cohorts varied between 26 and 36%. Dubin et al. observed a lower baseline ejection fraction of the systemic ventricle in non-responders (24 ± 11 vs. 32 ± 14%, p = 0.04). However, evaluation of this parameter in the CHD and paediatric 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 over echocardiography since this imaging tool does not rely on geometrical assumptions. Nevertheless, the majority of the CRT devices currently implanted are not compatible with magnetic resonance scanners and therefore, patient follow-up with this imaging technique is not feasible after device implantation.

Finally, CRT is indicated in patients with wide QRS complex. Current guidelines include width of the QRS complex >120 ms...
as a marker of electrical 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 paediatric 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 ventricle 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 min each. Compared with 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 paediatric patients with dilated cardiomyopathy have demonstrated the presence of LV mechanical dyssynchrony despite narrow QRS complex. These findings indicate that paediatric 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 paediatric 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 paediatric patients who will benefit from CRT.

Echocardiographic assessment of cardiac dyssynchrony

As mentioned before, prolonged QRS duration is the only criterion considered by current guidelines defining the presence of 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 transmitral 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 paediatric 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 right bundle branch block. Right ventricle filling time was calculated from the transtricuspid pulsed-wave Doppler spectral signal. At 17 months follow-up, RV filling time (normalized for RR interval) had increased from \( 45.1 \pm 6.5 \) to \( 50.0 \pm 6.1\% \) (\( P < 0.01 \)).

**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. Inter-ventricular mechanical delay 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). An IVMD \( > 40 \text{ ms} \) 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. Furthermore, in patients with pulmonary stenosis, the pulmonary pre-ejection interval may be prolonged. Little is known about IVMD cut-off values predicting response to CRT in paediatric and CHD patients. The available studies included too few patients precluding to draw robust conclusions regarding the performance of this dyssynchrony index to predict response to CRT. However, a consistent reduction in IVMD after CRT was reported in the majority of patients.

**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 adult patients 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.\textsuperscript{59} 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 ≥130 ms was proposed to predict response to CRT. In the CHD paediatric population several case reports and two small trials have used this index to evaluate the effects of CRT.\textsuperscript{24,39,41,60,61} For example, Tomaske and colleagues described six children with CHD and systemic LV failure who were treated with CRT.\textsuperscript{24} In these patients, SPWMD decreased from $312 \pm 24$ to $95 \pm 57$ ms ($P = 0.03$) after one month follow-up, along with an improved LVEF (from $41 \pm 6$ to $53 \pm 8\%$, $P = 0.03$) and a trend towards a decreased LV end-diastolic volume (from $70 \pm 22$ to $63 \pm 18$ mL/m\textsuperscript{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.\textsuperscript{17} Both pulsed-wave TDI and colour-coded TDI can be used to assess LV dyssynchrony. Unlike pulsed-wave TDI, colour-coded TDI can provide myocardial velocity tracings of two or more segments simultaneously (Figure 5). The feasibility and accuracy of colour-coded TDI to evaluate LV dyssynchrony have been extensively explored in studies on CRT in the adult population.\textsuperscript{17,62–64} One of the first indices was the time difference between peak systolic velocities of the septal and lateral LV wall. From the apical 4-chamber view, the time difference between peak systolic velocity of the basal septal and basal lateral walls was calculated: the

**Figure 6** Left ventricular dyssynchrony: TDI-derived radial and longitudinal strain. (A) Example of a post-operative tetralogy of Fallot patient with right ventricular dilatation and left ventricular dyssynchrony, assessed with TDI-derived radial strain. Left: Regions of interest are placed at the septal (blue) and posterior (yellow) wall of the left ventricle. Right: Radial strain (thickening of myocardium) curve. Dyssynchrony can be quantified by measuring time between peak radial strain at the septal and posterior walls (white arrow). A delay between the septal and posterior wall >130 ms indicates radial dyssynchrony.\textsuperscript{65} (B) Example of a patient with left ventricular dyssynchrony, assessed with TDI-derived longitudinal strain. Left: Regions of interest are placed at the inferior (yellow) and anterior wall (blue). Right: Longitudinal strain (shortening of myocardium) curve. Dyssynchrony can be quantified by measuring time between peak radial strain at the septal and posterior walls (white arrow).\textsuperscript{66} TDI, tissue Doppler imaging.
so-called septal-to-lateral wall delay. A septal-to-lateral wall delay ≥ 60 ms predicted response to CRT with a sensitivity of 76% and a specificity of 78%. Subsequently, a 4-segment model, including the basal segments of the septal, lateral, inferior and anterior walls was evaluated. The maximum delay between peak systolic velocities among the four LV walls was calculated. A delay ≥ 65 ms predicted clinical and echocardiographic response to CRT with high sensitivity (92%) and specificity (92%). Finally, Yu et al. proposed a 12-segment model, evaluating time to peak systolic velocity at six basal and six mid-myocardial segments of the LV. A standard deviation ≥ 32.6 ms predicted LV reverse remodelling after CRT with a sensitivity and specificity of 100%.

In paediatric populations, the usefulness of these indices has been demonstrated in several case reports and one small trial. Tomaske et al. 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 four-chamber view was 64 ± 10 ms and improved to 37 ± 8 ms after 1 month of CRT (P = 0.03), along with an improved LV systolic performance.

In addition to myocardial velocity, myocardial strain can be obtained from colour-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. TDI-derived strain has been evaluated in a paediatric study. Abd El Rahman et al. assessed TDI-derived longitudinal strain in 25 patients (median 19 years, range: 3–35 years) with tetralogy of Fallot and in 25 age-matched controls. The mean time to peak strain was assessed at the LV free wall (basal, mid and apical) as well as at the septum, and the mean septal-to-LV free wall time delay was calculated. Left ventricular dyssynchrony was defined as a septal-to-LV free wall delay two standard deviations above the mean observed in controls (> 25.8 ms). Accordingly, 52% of tetralogy of Fallot patients showed LV dyssynchrony. These patients had longer QRS duration (155 ± 19 vs. 136 ± 23 ms, P = 0.018) and an impaired LV performance compared with patients without dyssynchrony, as assessed with the Tei index (Tei index in patients with LV dyssynchrony: 0.5 ± 0.08, Tei index in patients without LV dyssynchrony: 0.38 ± 0.06, P = 0.004).

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 three-dimensional fashion (RT3DE).

Two-dimensional strain imaging or speckle-tracking strain imaging is a novel echocardiographic technique that permits multi-directional and angle-independent assessment of LV deformation. With this technique, the so-called speckles (natural acoustic markers equally distributed within the myocardium in 2D grey-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. Left ventricular dyssynchrony can be characterized by evaluating radial strain (thickening of the myocardium in the short-axis views) (Figure 7). At the

**Figure 7** Left ventricular dyssynchrony: two-dimensional speckle tracking. Example of a post-operative patient with atrioventricular septum defect and left ventricular dyssynchrony as assessed with two-dimensional speckle-tracking radial strain. **Left panel:** A region of interest can be indicated in a two-dimensional grey-scale image. The colours of the region of interest correspond with the colours of the time–strain curves in the right panel. **Right panel:** Time–radial strain curves of the different segments of the left ventricle. The time delay in peak radial strain between the antero-septal (yellow) and the posterior segments (purple curve) is 315 ms (> 130 ms), indicating the presence of significant left ventricular dyssynchrony.
mid-ventricular short-axis view of the LV, a maximum difference of \( \geq 130 \text{ ms} \) 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.\(^{68,69}\) 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.\(^{70,71}\) Tomaske \textit{et al.}\(^{24}\) investigated LV dyssynchrony by assessing 2D circumferential strain in six 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 1 month follow-up. Both dyssynchrony parameters decreased significantly at 1 month follow-up after CRT (maximum difference decreased from 201 ± 35 to 99 ± 23 ms, \( P = 0.03 \); the standard deviation decreased from 72 ± 14 to 40 ± 15 ms; \( P = 0.03 \)). Along with the mechanical resynchronization, the LVEF improved significantly at 1 month follow-up (from 41 ± 6 to 53 ± 8%, \( P = 0.03 \)).\(^{24}\) 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.\(^{72}\) In CHD and paediatric studies, the usefulness of this technique to identify the latest activated segment and to guide the LV lead placement has been also demonstrated.\(^{73,74}\)

Finally, RT3DE provides regional time–volume curves for the evaluation of LV dyssynchrony (Figure 8). Left ventricular 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 \textit{et al.}\(^{75}\) 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 \textit{et al.}\(^{34}\) performed RT3DE in

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**Figure 8** Left ventricular dyssynchrony assessed with real-time three-dimensional echocardiography. Example of a post-operative tetralogy of Fallot patient with left ventricular dyssynchrony, as assessed with real-time three-dimensional echocardiography. Contours are drawn at end-systole (A) and end-diastole in the short-axis view, four-chamber view, two-chamber view, and long-axis view. An automated tracking algorithm traces the myocardium throughout the cardiac cycle. The time–volume curves (C) are displayed, depicting instantaneous volume of each of the left ventricular segments (B), from which a systolic dyssynchrony index (standard deviation of time to minimum systolic volume of left ventricular segments) can be calculated. In this example, the systolic dyssynchrony index is 6.6%. A systolic dyssynchrony index >6.4% indicates left ventricular dyssynchrony.\(^{75}\) SDI, systolic dyssynchrony index.
10 single-ventricle patients who received multisite pacing post-operatively. At 48 h 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 paediatric and CHD patients. However, the predictive value of inter-ventricular dyssynchrony of the LV in CHD and paediatric patients may vary in the various anatomical subgroups. Furthermore, several factors such as previous pacing strategies, the presence and location of scar tissue and haemodynamic abnormalities may influence the CRT response.\(^{76}\) Additional trials are needed to establish cut-off values of LV dyssynchrony in CHD and paediatric 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.\(^ {33}\) assessed septal-to-lateral delay within the RV in the apical four-chamber view with colour-coded TDI in a patient with RV-systemic failure who was upgraded from conventional pacing to CRT. After 2 weeks, the RV septal-to-lateral delay decreased from 80 ms to completely synchronous contraction and exercise capacity improved significantly. In addition, Janousek et al.\(^ {29}\) evaluated intra-ventricular dyssynchrony of the RV with TDI-derived strain before and after CRT in eight patients with RV systemic failure. Right ventricle dyssynchrony was quantified by measuring the largest delay in time to peak strain between four mid-ventricular RV segments (septal, lateral, anterior, and posterior). After 4 days of CRT, RV dyssynchrony significantly reduced (from 138 ± 59 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,\(^ {77–79}\) 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 paediatric patients.\(^ {44–46}\) The population with CHD is growing, and this subgroup of patients has a high prevalence of heart failure during late follow-up.\(^ {11}\) Although some studies have demonstrated the beneficial effects of CRT in CHD and paediatric patients, there are several concerns. First, the population of CHD and paediatric patients included in the studies is highly heterogeneous, comprising various anatomical substrates (systemic LV, systemic RV, single-ventricle) and aetiologies of heart failure (chronic single-site ventricular pacing).\(^ {14–16}\) 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 paediatric heart failure population. Only a minority of CHD and paediatric patients included in studies on CRT fulfilled the adult guidelines of QRS > 120 ms, NYHA functional class III or IV and LVEF < 35%.\(^ {14–16}\) 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 paediatric patients who have the highest likelihood of response to CRT. However, the feasibility and performance of the various dyssynchrony parameters in CHD and paediatric 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 paediatric patients with heart failure. However, more studies are needed to establish appropriate guidelines for patient selection, taking into account the different anatomical subgroups.

**Funding**

A.E.H. has received a grant from the Willem-Alexander Kinder Fonds, Leiden, The Netherlands. A.A.W.R. is supported by a grant of the Netherlands Heart Foundation (2008T81).

**Conflict of interest:** J.J.B. has received grants from Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN, USA), Boston Scientific Corporation (Natick, MA, USA), Lanthens Medical Imaging (N. Billerica, MA, USA), St Jude Medical (St Paul, MN, USA), GE Healthcare (Milwaukee, WI, USA), and Edwards Lifesciences (Irvine, CA, USA). M.J.S. has received grants from Biotronik (Berlin, Germany), Medtronic (Minneapolis, MN), Boston Scientific Corporation (Natick, MA).

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