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ORIGINAL RESEARCH

Long-Term Outcome of Patients With Congenital Heart Disease Undergoing Cardiac Resynchronization Therapy

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BACKGROUND: Cardiac resynchronization therapy (CRT) is rarely used in patients with congenital heart disease, and reported follow-up is short. We sought to evaluate long-term impact of CRT in a single-center cohort of patients with congenital heart disease.

METHODS AND RESULTS: Thirty-two consecutive patients with structural congenital heart disease (N=30) or congenital atrioventricular block (N=2), aged median of 12.9 years at CRT with pacing capability device implantation, were followed up for a median of 8.7 years. CRT response was defined as an increase in systemic ventricular ejection fraction or fractional area of change by >10 units and improved or unchanged New York Heart Association class. Freedom from cardiovascular death, heart failure hospitalization, or new transplant listing was 92.6% and 83.2% at 5 and 10 years, respectively. Freedom from CRT complications, leading to surgical system revision (elective generator replacement excluded) or therapy termination, was 82.7% and 72.2% at 5 and 10 years, respectively. The overall probability of an uneventful therapy continuation was 76.3% and 58.8% at 5 and 10 years, respectively. There was a significant increase in ejection fraction/fractional area of change (P<0.001) mainly attributable to patients with systemic left ventricle (P=0.002) and decrease in systemic ventricular end-diastolic dimensions (P<0.05) after CRT. New York Heart Association functional class improved from a median 2.0 to 1.25 (P<0.001). Long-term CRT response was present in 54.8% of patients at last follow-up and was more frequent in systemic left ventricle (P<0.001).

CONCLUSIONS: CRT in patients with congenital heart disease was associated with acceptable survival and long-term response in ≈50% of patients. Probability of an uneventful CRT continuation was modest.

Key Words: cardiac resynchronization therapy ■ congenital heart disease ■ heart failure ■ long-term outcome

Discoordinate ventricular contraction is associated with wasted myocardial work and may lead to pathological ventricular remodeling, resulting in dyssynchronous heart failure (HF).[1,2] In adults with idiopathic or ischemic cardiomyopathy, cardiac resynchronization therapy (CRT) leads to improvement in ventricular function, increase in contraction efficiency, reverse ventricular remodeling, functional improvement, and decrease in HF events and overall mortality.[3,4] In this population, CRT is recommended as class IA indication in patients with chronic HF, QRS duration ≥150 ms, along with left bundle-branch block morphological features and left ventricular (LV) ejection fraction (EF) ≤35% who remain in New York Heart Association (NYHA) functional class 2, 3, and ambulatory 4 despite adequate medical treatment.[5]

CRT has been reported as a promising therapeutic option in patients with congenital heart disease (CHD) and HF associated with ventricular electromechanical dyssynchrony.[6] HF is the leading cause of mortality

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CLINICAL PERSPECTIVE

What Is New?

- Follow-up exceeded by far any previously published multicenter or single-center reports, showing a different long-term cardiac resynchronization therapy response rate in patients with systemic left ventricle and right/functionally single ventricle.

What Are the Clinical Implications?

- Demonstration of potentially important role of the electrical activation delay within the systemic ventricle when searching for optimal pacing site.
- Modest overall probability of an uneventful long-term cardiac resynchronization therapy continuation, reflecting the complexity of device therapy in this diverse population.

Nonstandard Abbreviations and Acronyms

CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy with defibrillation capability
FAC	fractional area of change
NYHA	New York Heart Association
SV	functionally single ventricle

in adult CHD along with sudden death.[7,8] The marked heterogeneity of patients, including those with complex CHD, systemic right ventricle (RV)/functionally single ventricle (SV), history of repeated cardiac surgery, impaired hemodynamics on multiple levels (pressure/volume overload, functional/structural myocardial injury, including surgical scars, altered myocardial architecture, impairment in diastolic filling, presence of atrioventricular valve regurgitation, and specific conditions of single ventricular physiological features),[9,10] along with high diversity in age and body size, precludes simple conclusions from the available observational studies as well as extrapolation of data from adult CRT series. In addition, a different spectrum of electromechanical dyssynchrony has been reported in patients with CHD undergoing CRT, dominated by ventricular mechanical discoordination associated with conventional ventricular pacing or right bundle-branch block.[11] Prospective randomized studies evaluating CRT in children and patients with CHD are not available. The PACES/HRS (Pediatric & Congenital Electrophysiology Society/Heart Rhythm Society) expert consensus statement on the recognition and management of arrhythmias in adult CHD[12] tried to specify CRT indications for the 3 different anatomic conditions: patients with systemic left, right, and single ventricle. CRT criteria were mainly drawn from adult idiopathic and ischemic cardiomyopathy guidelines, and specific recommendations were mainly based just on evidence C levels. Favorable short- to mid-term outcomes of CRT were previously reported.[13–15] However, data on long-term efficacy and therapy complications are scarce.[16] Thus, any further information clarifying the position of CRT in the life-long management of patients with congenital disease is warranted. The aim of the study was to retrospectively evaluate long-term outcome in a single-center cohort of patients with CHD undergoing CRT.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

Thirty-two consecutive patients (15 boys and 17 girls; Table 1) with structural CHD (N=30) or congenital complete atrioventricular block (N=2) who received CRT between 2002 and 2014 in a single tertiary care center providing complete pediatric cardiovascular care for the whole territory of the Czech Republic (10.5 million inhabitants) were followed up prospectively. The median age at implantation was 12.9 (interquartile range [IQR], 5.9–17.9) years. Systemic ventricle was left in 14 of 32 (43.8%), right in 14 of 32 (43.8%), and functionally single in 4 of 32 (12.5%) patients. Most patients (24/32; 75.0%) had complete atrioventricular block (spontaneous in 7 [patients 6, 10, 11, 18, 24, 25, and 28; Table S1] and surgical in 17 [patients 1–5, 7–9, 12, 15, 17, 21, 22, 26, 27, 29, and 30; Table S1]). Of the 24 patients, 19 (patients 2, 4–6, 8–12, 15, 18, 21, 22, 24–28, and 30; Table S1) were conventionally paced from the subpulmonary ventricle for a median of 7.4 (IQR, 3.8–10.0) years before CRT. Four (patients 1, 3, 17, and 29; Table S1) of the 24 patients with complete atrioventricular block received a primary CRT device after having been paced by temporary pacing wires from the subpulmonary ventricle for acute surgical atrioventricular block and developed systemic ventricular dysfunction. One of the 24 patients (patient 7; Table S1) with atrioventricular block received a primary CRT device as prevention of pacing-induced systemic ventricular dysfunction. The remaining 8 of 32 patients had either right (N=6 [patients 16, 19, 20, 23, 31, and 32; Table S1]) or left bundle-branch block (N=2 [patients 13 and 14; Table S1]) associated with systemic RV (N=4

Table 1. Patient Data

Variable	Age, y	FUP, y	Surgery Before CRT	Surgery at CRT	Surgery After CRT	Conventional Pacing	CRT System	NYHA Class Before CRT	NYHA Class at Last FUP	EF/FAC Before CRT, %	EF/FAC at Last FUP, %	EDDz Before CRT	EDDz at Last FUP	CRT Response at Last FUP	Outcome
All patients (N=32)															
Median (IQR)	12.9 (5.9–17.9)	8.7 (4.5–11.2)	Yes=25 No=7	Yes=11 No=21	Yes=7 No=25	Yes=19 No=13	Epicardial=19 Transvenous=4 Mixed=8	2.0	1.25	28.8 (20.6–34.9)	39.7 (32.0–44.6)	4.4 (2.2–7.8)	1.8 (0.4–3.7)	Yes=17 No=16	Alive=28 SCD=4 CRT terminated=7
Systemic left ventricle (N=14)															
Median (IQR)	10.7 (3.5–14.0)	7.7 (4.2–10.9)	Yes=11 No=3	Yes=5 No=9	Yes=3 No=11	Yes=9 No=5	Epicardial=11 Transvenous=1 Mixed=2	2.0	1.0	29.5 (23.6–38.2)	50.2 (40.5–55.5)	4.8 (0.8–7.4)	0.5 (0.1–2.7)	Yes=12 No=2	Alive=13 SCD=1 CRT terminated=5
Systemic right ventricle (N=14)															
Median (IQR)	17.6 (10.3–26.1)	9.3 (6.2–11.2)	Yes=10 No=4	Yes=5 No=9	Yes=3 No=11	Yes=9 No=5	Epicardial=5 Transvenous=3 Mixed=6	2.0	1.0	26.2 (22.5–33.0)	33.2 (29.7–37.5)	3.5 (2.2–5.8)	2.4 (1.1–3.2)	Yes=3 No=11	Alive=12 SCD=2 CRT terminated=2
Functionally single ventricle (N=4)															
Median (IQR)	9.1 (3.3–16.8)	6.0 (4.3–8.0)	Yes=4 No=0	Yes=1 No=3	Yes=1 No=3	Yes=1 No=3	Epicardial=4 Transvenous=0 Mixed=0	2.5	2.5	22.7 (15.9–30.8)	25.7 (21.7–31.5)	8.4 (8.0–11.0)	6.4 (5.1–7.9)	Yes=2 No=2	Alive=3 SCD=1

CRT indicates cardiac resynchronization therapy; EDDz, systemic ventricular end-diastolic dimension (*z* score); EF, ejection fraction; FAC, fractional area of change; FUP, follow-up; IQR, interquartile range; NYHA, New York Heart Association; and SCD, sudden cardiac death.

[patients 16, 19, 20, and 23; Table S1]), LV (N=2 [patients 13 and 14; Table S1]), and single ventricular (N=2 [patients 31 and 32; Table S1]) dyssynchrony. The indication for CRT in 31 of 32 patients (except patient 7; Table S1) was the presence of intraventricular and interventricular electromechanical dyssynchrony along with a clinically relevant systemic/single ventricular dysfunction associated with symptoms and increased NYHA class ≥2 in most (Table S1).[12] Most patients (25/32; 78.1%) were on chronic HF medication before CRT. The study was approved by the institutional review committee, and the subjects gave informed consent with the study.

Follow-Up

Acute CRT testing was performed by echocardiography at the time of device implantation by switching between the baseline and CRT rhythm (N=22). Patients were further followed up prospectively in 6-month intervals after implantation or more frequently if clinically indicated for median of 8.7 (IQR, 4.5–11.2 [range, 2.4–14.4]) years on functional CRT, with a total of 265.1 patient-years available for analysis. Clinical and pacing system examination, 12-lead ECG, and echocardiographic measurements of systemic ventricular function and dimensions were performed. Data before CRT, 6 to 12 months after CRT, and at the end of follow-up on functional CRT were used for analysis. CRT response was evaluated in 31 of 32 patients implanted because of the presence of systemic ventricular dysfunction at baseline. Positive long-term CRT response was defined as presence of an increase in systemic ventricular EF or fractional area of change (FAC) by >10 EF/FAC units and improved or unchanged NYHA functional class regardless of the presence of associated or subsequent cardiac interventional procedures. Data on systolic ventricular function, allowing for CRT response classification, were available in all 31 eligible patients at the end of follow-up and in 25 of 31 patients 6 to 12 months after CRT.

Electrocardiographic Data

QRS duration was measured as the longest interval in any of the 12 leads. Baseline QRS morphological features were observed with specific attention to the late component reflecting delayed activation of the dyssynchronous systemic ventricle and visible as bundle-branch block pattern. Local activation time was measured between the QRS onset and local electrogram obtained from the systemic ventricular pacing lead during baseline rhythm and expressed as absolute q-V interval and as percentage of QRS duration, respectively. Disappearance or significant attenuation of the bundle-branch block pattern after CRT was documented.

Echocardiographic Data

The following echocardiographic measurements and calculations were performed using the Vivid-GE equipment and the EchoPac 113.0.3 workstation (both from GE/Vingmed, Horten, Norway):

1. End-diastolic and end-systolic dimensions of the systemic ventricle were measured at the point of peak diastolic systemic ventricular free wall outward motion and peak systolic inward motion, respectively, and expressed as z-score indexed to a normal systemic LV.[17] In patients with systemic LV, EF was measured using the biplane Simpson method. In case of systemic RV or SV, FAC was calculated from the apical 4-chamber view.
2. Systemic ventricular filling time (expressed as a percentage of cycle length) was measured in apical 4-chamber view using pulse-wave Doppler analysis of the flow across the systemic atrioventricular valve.
3. Maximum dP/dt (derivative of pressure over time) of the systemic ventricle was measured in patients who had systemic atrioventricular valve regurgitation from the slope of the regurgitation jet between 1 and 3 m/s using pulsed or continuous wave Doppler.
4. Aortic velocity-time integral was calculated as a measure of cardiac output, placing pulsed Doppler sample volume in systemic ventricular outflow tract below the aortic valve.
5. Septal to lateral mechanical delay was measured from the parasternal short-axis M mode.[18]
6. Interventricular mechanical delay was calculated as the difference between the left and right ventricular preejection period.

Three consecutive cardiac cycles with simultaneous ECG recording to allow for identification of QRS onset were analyzed, and the results were averaged. In case of the acute CRT testing, few cardiac cycles were allowed for stabilization before taking the echocardiographic measurements in each pacing mode (baseline and CRT on).

Statistical Analysis

Data are presented as mean (SD) or as median (25%/75% quartiles), as appropriate, according to the mode of distribution. Differences in continuous variables among groups of patients were evaluated by 2-tailed *t* test or Mann-Whitney rank sum test, as appropriate. Paired comparisons were performed by paired *t* test. Multiple comparisons between different treatment groups were performed by 1-way ANOVA, followed by pair-wise multiple comparisons using the Holm-Sidak method for normally distributed data, or by the Kruskal-Wallis 1-way ANOVA on ranks, followed by pair-wise multiple comparisons by the Dunn method

in case of absence of normal distribution. Differences in proportions between 2 groups were tested by the Fisher exact test. Correlation between 2 variables was evaluated by linear regression. Actuarial survival probability was computed using the Kaplan-Meier method, and the log-rank statistic was used for the detection of differences between 2 groups. Values of $P<0.05$ were regarded as significant. All statistical analysis was performed using the SigmaPlot for Windows Version 12.0 (Systat Software Inc).

RESULTS

CRT Procedures

All patients received primarily a CRT with pacing capability system. Four systems were implanted transvenously, 20 were placed by thoracotomy using epicardial pacing leads, and 8 used mixed lead systems with the transvenous ventricular lead placed in the subpulmonary ventricle and an epicardial lead on the systemic ventricle. Ventricular lead connected to the LV output of the pulse generator was systematically placed in the area of late ventricular activation of the systemic ventricle, as presumed from QRS morphological features, and measured subsequently intraoperatively. Local activation time at the site of "LV lead" implantation (q-V interval) was measured during implantation in 25 of 32 patients (13/14 with systemic LV and 12/18 with systemic RV/SV) and equaled median 150 (IQR, 130–160) ms or 94.0% (IQR, 85.3%–101.5%) of QRS duration, respectively, without significant difference between patients with LV and RV/SV. The "RV lead" was implanted in the subpulmonary chamber. In case of a preexisting conventional pacemaker, the original lead was connected to the RV output. CRT implantations were associated with additional cardiac surgery in 11 of 32 (34.4%) patients (Table 1).

Clinical Follow-Up

Freedom from cardiovascular death, HF hospitalization, or new transplant listing (Figure 1) was 92.6% and 83.2% at 5 and 10 years, respectively, and did not differ significantly between the LV and RV/SV groups (P=0.544). Four patients died suddenly during follow-up with a functional CRT system (details are given in Table S1): patient 4 with a history of intra-atrial reentrant tachycardia, patients 20 and 31 with recently decompensated HF and documented electromechanical dissociation, and patient 27 without known tachyarrhythmias. Hospitalization for HF was necessary in 2 patients (patients 20 and 31; Table S1). None of the patients was listed or underwent heart transplant while on CRT. Upgrade to CRT with defibrillation capability (CRT-D) was performed in 1 patient as a primary prevention because of low EF (patient 17; Table S1). During follow-up, pharmacologic therapy for chronic HF could be discontinued in 2 of 25 patients. Six patients underwent different revision cardiac surgical procedures (Table S1).

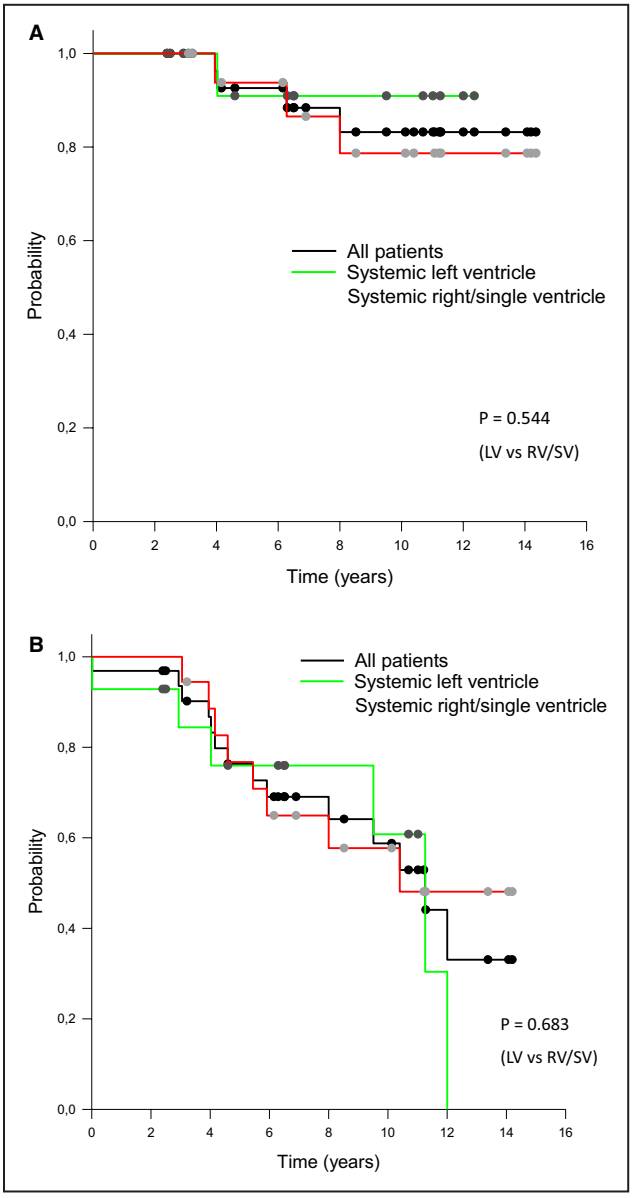

Figure 1. Clinical follow-up and pacing system survival.
A, Survival probability after cardiac resynchronization therapy (CRT) system implantation: freedom from cardiovascular death, heart failure hospitalization, and new transplant listing. **B**, Overall probability of an uneventful CRT continuation: freedom from death, heart failure hospitalization, new heart transplant listing, CRT termination, or surgical revision of the pacing system other than elective battery replacement. LV indicates left ventricle; RV, right ventricle; and SV, functionally single ventricle.

Acute CRT Testing

Data on acute CRT testing were available in 22 of 32 patients (Table 2). Maximum dP/dt of the systemic ventricle, aortic velocity-time integral, and systemic ventricular

Table 2. Acute CRT testing (N=22)

Parameter	Maximum dP/dt, mm Hg/s			Aortic Velocity Time Integral, cm			Systemic Ventricular Filling Time, % CL		
	All	Responders	Nonresponders	All	Responders	Nonresponders	All	Responders	Nonresponders
CRT off	529.0 (431.0–793.5)	485.0 (416.0–648.0)	538.0 (483.0–830.3)	13.6 (11.4–19.0)	12.8 (8.8–15.1)	15.3 (12.8–19.6)	42.0 (35.7–46.2)	38.1 (34.6–43.0)	44.2 (40.3–49.2)
CRT on	736.0 (612.0–1001.0)	736.0 (681.0–1288.0)	656.0 (580.8–957.5)	14.2 (15.9–22.4)	13.7 (10.0–17.7)	19.5 (13.7–25.7)	47.3 (41.1–53.7)	44.2 (35–48.9)	51.1 (42.7–58.1)
P value	<0.001	0.200	0.193	<0.001	0.535	0.303	<0.001	0.226	0.169

Data are given as median (interquartile range). dP/dt indicates derivative of pressure of the systemic ventricle over time; CL, cycle length; and CRT, cardiac resynchronization therapy.

filling time all improved during acute CRT evaluation while CRT switched on. Magnitude of improvement did not correlate with baseline QRS duration, decrease in QRS duration after CRT, or q-V/QRS ratio. The number of measurements was too low to evaluate the impact of systemic ventricular morphological features.

Long-Term CRT Response

CRT response was achieved in 60.0% of patients at 6 to 12 months (data available in 25/31 eligible patients) and in 54.8% of patients at last follow-up on CRT. A significant difference in response rate was evident between patients with systemic LV and RV/SV at both 6 to 12 months (84.6% versus 33.3%; P=0.015) and last follow-up (92.3% versus 27.8%; P<0.001). Of 15 patients with initial (6–12 months) CRT response, 4 turned out to be nonresponders on the long-term, and 5 of 10 initial nonresponders converted to responders at last follow-up. One of these 9 crossover patients underwent subsequent cardiac surgery between the 6 to 12 months and last follow-up dates (patient 32; Table S1). The percentage of patients with long-term CRT response during the study follow-up is shown in Figure 2. In 13 patients with available data, increase in systemic ventricular dP/dt during acute CRT testing was significantly higher in long-term CRT responders as opposed to nonresponders: mean, 78.0% (SD, 46.3%) versus 27.0% (SD, 20.3%) (P=0.016). None of the other variables (namely, baseline QRS duration, decrease in QRS duration after CRT, q-V/QRS ratio, and change in the aortic velocity-time integral or increase in systemic ventricular filling time during acute CRT testing) was predictive of long-term efficacy.

NYHA class improved significantly from a median 2.0 before CRT to 1.5 at 6 to 12 months and to 1.25 at last follow-up (P<0.001). The proportion of patients with NYHA class 1 increased significantly at both 6 to 12 months and at the end of CRT follow-up (P=0.001 and P<0.001, respectively), mainly attributable to patients with systemic LV (Figure 3).

There was a significant increase in EF/FAC, mainly attributable to patients with systemic LV (P=0.002), and decrease in systemic ventricular end-diastolic dimensions after CRT (Figure 4A and 4B).

Electromechanical Dyssynchrony

All patients had a wide QRS complex with bundle-branch block morphological features at baseline. With one exception (patient 14; Table S1), their QRS pattern corresponded with a major electrical activation delay within the failing dyssynchronous ventricle. Disappearance or significant attenuation of the respective bundle-branch block pattern with elimination of the late activation component after CRT was documented in 31 of 32 (96.9%) patients and was accompanied by a significant decrease in QRS duration from median

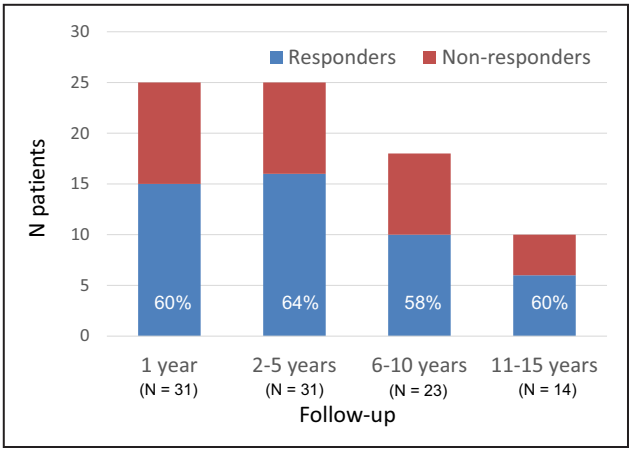

Figure 2. Proportion (percentage) of long-term responders during the study follow-up.
Only patients with available data are included. "N" in parenthesis indicates total number of patients followed up on cardiac resynchronization therapy at each particular period.

160 ms before CRT to 120 ms at 6 to 12 months on CRT and to 130 ms at the end of follow-up (P<0.001; Table 3). Mechanical dyssynchrony indexes were also significantly attenuated by CRT (Table 3).

CRT Complications and Termination

Surgical revision of the pacing system had to be performed in 3 patients (revision for bleeding during the early postoperative course in 1 patient [patient 5; Table S1] and replacement of the lead adaptor connecting 2 systemic ventricular unipolar pacing leads in 2 patients [patients 15 and 18; Table S1]). Pacing system had to be extracted in 1 patient after 37 months on CRT because of infection, and conventional dual-chamber pacing was initiated (patient 16; Table S1). CRT was terminated for various reasons in 7 of 32 patients at a median (IQR) 6.5 (4.0–10.9) years after implantation (Table 4). Hemodynamic and functional data in those patients are summarized in Figure 5 and show a nonuniform response to therapy termination. Freedom from CRT complications leading to surgical system revision (elective generator replacement excluded) or therapy termination was 82.7% and 72.2% at 5 and 10 years, respectively, and did not differ significantly between LV and RV/SV groups. The overall probability of an uneventful CRT continuation, including death, HF hospitalization, new heart transplant listing, therapy termination, and surgical revision other than elective generator replacement (Figure 1), was 76.3% and 58.8% at 5 and 10 years, respectively, and did not differ significantly between the LV and RV/SV groups (P=0.683).

DISCUSSION

In this report, we tried to summarize single-center experience of up to 14 (median, 8.7) years of CRT. Such

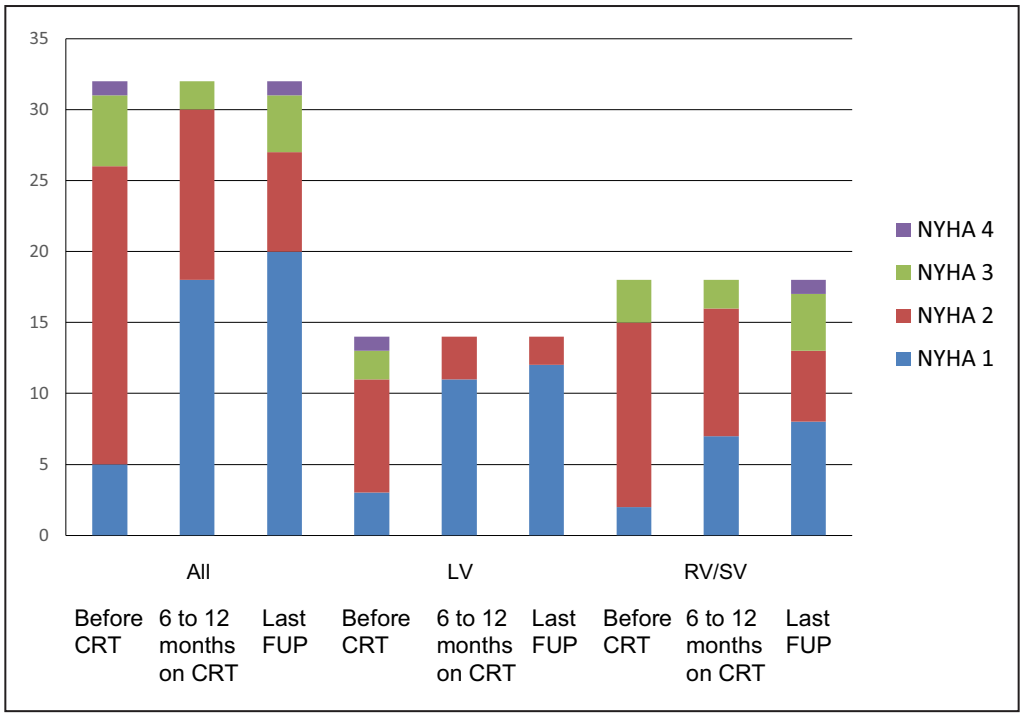

Figure 3. Number of patients according to New York Heart Association (NYHA) class.
CRT indicates cardiac resynchronization therapy; FUP, follow-up; LV, left ventricle; RV, right ventricle; and SV, functionally single ventricle.

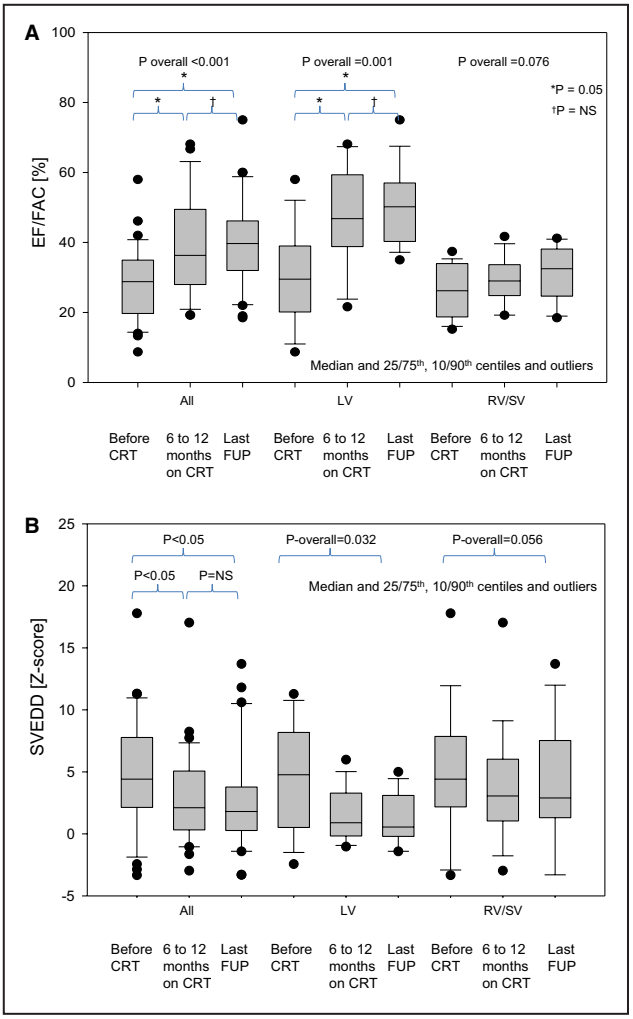

Figure 4. Systemic ventricular function and dimension.
A, Systemic ventricular ejection fraction (EF) or fractional area of change (FAC). **B**, Systemic ventricular end-diastolic dimension (SVEDD). CRT indicates cardiac resynchronization therapy; FUP, follow-up; LV, left ventricle; NS, not significant; RV, right ventricle; and SV, functionally single ventricle.

follow-up exceeds by far any previously published multicenter or single-center reports.[13–16,19]

CRT indication was based on the finding of a major electrical activation delay within the systemic ventricle, as reflected by the surface QRS morphological features and confirmed by the measurements of long local activation times at the site of systemic CRT lead implantation. Such data have not been presented before in patients with CHD and may be helpful to find optimal pacing sites intraoperatively. Using such approach, we could observe significant and lasting shortening of the QRS complex after CRT. Specifically, late activation corresponding with the systemic ventricle was abolished, as proved by the disappearance or significant attenuation of bundle-branch block pattern. Placement of CRT leads at the site of late activation has been previously shown to correlate with CRT efficacy.[20] We have, however, not found any correlation between the q-V interval at the site of CRT lead implantation and short-term or long-term contractility indexes. This may be explained by the fact of proper lead placement in areas of late activation in all patients, supported by the improvement of all measured parameters during acute CRT testing (Table 2). It could be speculated, based on the report of Singh,[20] that the correlation of q-V/QRS ratio with long-term CRT efficacy can also be influenced by the pathophysiologic substrate (type of systemic ventricle or previous conventional pacing). The number of measurements did not, however, allow for valuable statistics. As shown in previous reports, the presence of systemic LV[21] and prior conventional pacing[14] were associated with the best response to CRT.

Being aware of the difficulties in CRT response definition (short follow-up and mainly retrospective character in previous studies and limited number of subjects with large heterogeneity of CHD population) and considering the absence of generally accepted and uniform criteria to define CRT responders in children and/or CHD population, we aimed, in conformity with a recent article,[22] to assess not only echocardiographic but also functional parameters (NYHA class), along with the inclusion of data on mortality and HF hospitalization in statistical analysis.[23] The systolic function of the systemic ventricle (EF/FAC) was the major parameter of echocardiographic CRT response evaluation in several studies.[13–15,24] Long-term CRT response is likely to be influenced by many intervening factors, mainly additional cardiac interventions and spontaneous changes in hemodynamics and myocardial function. In observational studies, these factors cannot be dissociated from the CRT effects alone. Marked heterogeneity of pediatric CHD population limits significantly the possibility to create a valid control group and to raise general conclusions about the value of CRT alone. However, along with our data on long-term CRT response (focusing on both technical and

Table 3. Electromechanical Dyssynchrony

Parameter	QRS Duration, ms (N=32)	Interventricular Mechanical Delay, ms (N=23)	Septal to Posterior Wall Motion Delay, ms (N=19)
Before CRT	160 (150–180)	50 (40–69)	245 (75 to 295)
6–12 mo after CRT	120 (100–135)	27 (12–53)	–5 (–26 to 70)
P value	<0.001	<0.001	<0.001

Data are given as median (interquartile range). CRT indicates cardiac resynchronization therapy.

Table 4. CRT Termination (N=7)

Patient No.*	CRT Duration, y	Reason for CRT Termination	FUP After CRT Termination, y	Outcome	Reintervention After CRT Termination	Comment
1	11.3	Ventricular lead exit block	3.3	Alive	Re-CRT+surgery	New epicardial pacing lead on LV apex during prosthetic mitral valve replacement (3.0 y after CRT termination)
2	9.5	Ventricular lead exit block	3.5	Alive	0	
8	2.9	Ventricular lead exit block	5.0	Alive	0	
9	6.5	Restitution of atrioventricular conduction	8.1	Alive	0	
10	12.0	Ventricular lead exit block	2.9	Alive	0	
16	3.1	Infection	8.1	Died	ICD implantation	CPR 8 y after CRT termination; listed subsequently to HT and ICD implanted, died after 6 wk because of low cardiac output
28	6.52	Ventricular lead exit block	7.1	Alive	0	

CPR indicates cardiopulmonary resuscitation; CRT, cardiac resynchronization therapy; FUP, follow-up; Re-CRT, repeated CRT; HT, heart transplant; ICD, implantable cardioverter-defibrillator; and LV, left ventricle.

*Patient No., patient number according to Table S1.

clinical aspects), we aimed to describe a comprehensive long-term management outcome in a patient cohort with CRT. In the presented study, long-term CRT response was not sustained in all patients and significant differences exist between the response rate of patients with systemic LV and RV/SV, despite a favorable response in both groups during acute CRT testing at the time of implantation. The dependence of CRT efficacy on underlying ventricular anatomical features has been already described previously.[6,13–15]

The fact that most (19/32) of our patients had been conventionally paced from the subpulmonary ventricle before CRT may limit the applicability of our conclusions to the group of patients with CHD without prior pacing. However, as shown by several authors,[13–15] previous conventional pacing was the most prevalent indication to CRT in the pediatric and CHD population.

We included patients with unchanged NYHA class to define those with positive long-term CRT response. Five patients were in NYHA class 1 at the time of CRT indication, and another 22 of 32 were in NYHA class 2. This reflects a proactive approach to CRT in CHD population,[12,13,21] which, on the other side, limits the inclusion of improvement in NYHA class to define CRT response. Poor initial NYHA class was previously shown to be the risk factor for nonresponse to CRT in these patients.[14]

Our data show better improvement in systemic ventricular dP/dt during acute CRT testing in long-term CRT responders as opposed to nonresponders. This is in line with a previous report correlating a short-term CRT response with long-term efficacy and enabling CRT effect testing before implantation.[16] Such testing may be specifically helpful in patients with complex anatomical features (systemic RV/SV) and difficult surgical approach to CRT lead placement, allowing for rational assessment of potential CRT benefit as a part of the procedure planning.

The proportion of patients with CRT-D was lower than referred by other studies with either adult[19] or both pediatric/adult CHD population,[24] reporting 79% and 30% of implanted devices with defibrillation capacity, respectively. Of patients undergoing CRT-D, 20% received appropriate implantable cardioverter-defibrillator discharges and none of them received an inappropriate shock in the latter study. CRT-D devices were not primarily used in our patient group, reflecting mainly unclear indications for primary preventive implantable cardioverter-defibrillator therapy in children. However, 2 of 4 deaths may have potentially been prevented by a CRT-D device in this patient cohort.

Chubb et al[24] report an 85% survival of all leads at 5 years, which is in accordance with our cohort at comparable length of the follow-up. Our study went much further in time and showed that both long-term freedom from surgical revisions of the CRT system as well as overall probability of an uneventful CRT continuation were modest. Such finding reflects the complexity of device therapy in this diverse population. Freedom from CRT system dysfunction, referred by Koyak et al,[19] was ≈60% at 8 years, which is well comparable to our long-term data, but their median follow-up was much shorter (2.6 years).

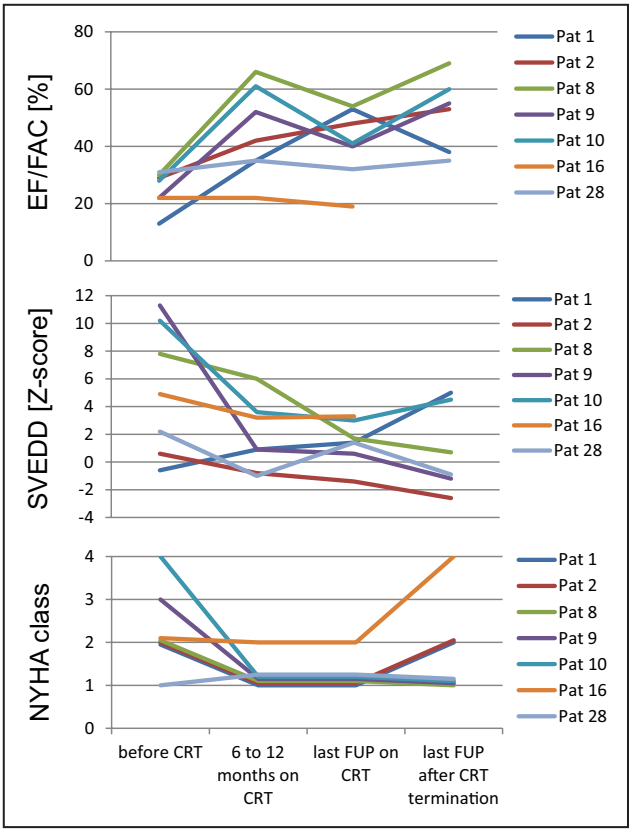

Figure 5. Hemodynamic and functional data in patients (Pats) with cardiac resynchronization therapy (CRT) termination.
EF indicates ejection fraction; FAC, fractional area of change; FUP, follow-up; NYHA, New York Heart Association; and SVEDD, systemic ventricular end-diastolic dimension.

The main contribution of this study to the current knowledge on CRT in children and patients with CHD:

1. Demonstration of potential important role of the electrical activation delay within the systemic ventricle when searching for the optimal pacing site, supported by measurements during acute CRT testing at the time of implantation.
2. Follow-up exceeding by far any previously published multicenter or single-center reports, showing a different long-term CRT response rate in patients with systemic LV and RV/SV, thus validating the results of previous reports with much shorter follow-up.[13–15]
3. Modest overall probability of an uneventful long-term CRT continuation, reflecting the complexity of device therapy in this diverse population.

Limitations

The main limitation of this study is its observational nonrandomized character and limited number of patients in subgroups based on the systemic ventricular morphological features. Considering the diversity of intervening factors influencing the long-term CRT response and the absence of the control group, direct conclusions on the isolated impact of CRT on long-term disease course cannot be drawn. Sustained improvement of systemic ventricular function after CRT is, however, likely to correlate with positive modification of the course of CHD.[25] Because of the relatively long follow-up in this study, further factors are likely to intervene with CRT effect, including revision cardiac surgery, development of hemodynamic residua, and myocardial dysfunction. All those could not be exactly quantified. Long-term CRT response was defined as improvement in systemic ventricular systolic function and improved or unchanged NYHA class. Although a matter of discussion, this is in line with the article of Daubert et al.[22] Also, the number of patients and the heterogeneity of structural substrates make a meaningful analysis of interim data between 6 and 12 months and last follow-up on CRT impossible. The authors have at least tried to express the time course of major clinical events using survival curves (Figure 1). Further limitations lie in the inaccuracy of echocardiographic measurement of systemic ventricular function, specifically in patients with the systemic right or single ventricle. Parameters reflecting functional consequences of systemic ventricular dysfunction, such as NT-proBNP (N-terminal pro-B-type natriuretic peptide) levels and exercise stress data, were not systematically available. Further studies, optimally randomized (feasibility?), prospective, and multicenter, should follow in close future to overcome main limitations, as listed above.

CONCLUSIONS

CRT in pediatric patients and patients with CHD was associated with a high freedom from a composite end point consisting of cardiovascular death, HF hospitalization, or new transplant listing. Long-term improvement in systemic ventricular function, along with favorable functional NYHA class, was present in about 50% of patients. The response rate was significantly higher in patients with systemic LV and correlated with contractility improvement during acute CRT testing at the time of implantation. Overall probability of an uneventful long-term CRT continuation with absence of device complications necessitating surgical revision or therapy termination was, however, modest, reflecting the complexity of device therapy in this diverse population.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. Patients: clinical data.

Pat. No	Age (yrs)	FUP (yrs)	Diagnosis	Surgery prior to CRT	Surgery at CRT	Surgery after CRT	Conventional pacing	CRT system	NYHA before CRT	NYHA at last FUP	EF/FAC before CRT (%)	EF/FAC at last FUP (%)	EDDz before CRT	EDDz at last FUP	CRT response at last FUP	Outcome
Systemic left ventricle																
1	0.4	11.3	AVSD-I	COR, MVR	0	VSD closure	No	Epi	2.0	1.0	13.0	53.3	-0.6	1.4	Yes	Alive, CRT terminated
2	6.4	9.5	AVSD-C	COR	MVR	0	Yes	Epi	2.0	1.0	28.6	47.8	0.6	-1.4	Yes	Alive, CRT terminated
3	17.3	11.0	AS, BE	0	AVR	0	No	Mixed	2.0	1.0	42.0	60.0	5.7	0.5	Yes	Alive
4	11.6	4.0	PA/IVS	COR	0	BCPA, CND	Yes	Epi	2.0	2.0	8.7	75.0	9.4	-1.4	Yes	SCD
5	14.7	12.4	VSD, MS	COR, MVR	MVR	0	Yes	Mixed	2.0	2.0	46.1	60.0	3.5	-1.1	Yes	Alive
6	12.6	8.9	ASD	COR	0	0	Yes	Epi	1.0	1.0	30.0	39.4	6.4	3.4	No	Alive

7	9.9	10.7	AVSD-C	COR, MVR	0	0	No	Epi	1.0	1.0	58.0	41.0	1.4	5.0	No	Alive
8	1.4	2.9	VSD	COR	0	Ross	Yes	Epi	2.0	1.0	30.0	54.0	7.8	1.7	Yes	Alive, CRT terminated
9	2.6	6.5	VSD	COR	0	0	Yes	Epi	3.0	1.0	22.0	40.4	11.3	0.6	Yes	Alive, CRT terminated
10	3.4	12.0	CCAVB	0	0	0	Yes	Epi	4.0	1.0	27.6	41.3	10.2	3.0	Yes	Alive, CRT terminated
11	14.1	2.4	CCAVB	0	0	0	Yes	Epi	1.0	1.0	29.0	40.0	5.7	3.9	Yes	Alive
12	17.7	6.3	PA/VSD	COR	CND	0	Yes	Epi	3.0	1.0	14.0	35.0	0.3	0.5	Yes	Alive
13	3.7	2.5	VSD, MR	COR	MVR	0	No	Epi	2.0	1.0	38.0	56.0	-2.4	0.1	Yes	Alive
14	13.7	4.6	DORV	COR	0	0	No	TV	2.0	1.0	38.0	52.6	3.9	0.2	Yes	Alive
Systemic right ventricle																
15	22.4	14.4	TGA	Senning	0	0	Yes	Mixed	2.0	2.0	23.1	32.0	3.7	2.9	No	Alive

16	13.1	3.1	TGA, VSD	Senning, PAB	dePAB	0	No	Epi	2.0	2.0	22.3	19.0	4.9	3.3	No	Alive, CRT terminated
17	16.8	6.9	CTGA, VSD, PS	0	COR (sRV)	0	No	Epi	2.0	1.0	23.1	37.5	11.3	13.7	Yes	Alive
18	9.6	10.4	CTGA, VSD	0	COR (sRV)	0	Yes	Epi	2.0	1.0	17.5	40.6	2.2	2.9	Yes	Alive
19	18.3	11.1	DORV, VI, PS	COR (sRV), TVR	0	0	No	TV	2.0	3.0	37.4	22.2	6.8	2.9	No	Alive
20	29.2	5.9	TGA	Mustard	0	0	No	Mixed	3.0	4.0	18.9	29.1	3.0	1.9	No	SCD
21	28.8	10.1	DORV, VI, PS	COR (sRV)	0	0	Yes	TV	2.0	1.0	26.2	40.9	3.3	-3.3	Yes	Alive
22	6.9	13.4	DORV, VI	COR (sRV)	0	0	Yes	Mixed	2.0	1.0	35.1	33.3	2.1	-3.3	No	Alive
23	18.5	11.2	CTGA, VSD, PS	COR (sRV)	0	PVR, TVR	No	Mixed	2.0	1.0	29.9	34.5	-2.9	-1.0	No	Alive
24	8.6	14.2	CTGA	0	TVR		Yes	Epi	1.0	1.0	35.0	41.2	6.1	1.0	No	Alive

25	43.7	3.2	CTGA, PS	0	0	ASD closure	Yes	TV	2.0	1.0	18.2	25.3	3.9	10.3	No	Alive
26	27.3	8.5	CTGA, VSD	COR, TVR,	0	0	Yes	Mixed	2.0	3.0	26.2	37.0	-3.3	1.6	No	Alive
27	12.2	8.0	TGA, VSD	Senning	PAB	0	Yes	Mixed	2.0	2.0	33.7	33.0	6.1	10.6	No	SCD
28	4.5	4.2	CTGA, VSD, PS	COR (sRV)	0	0	Yes	Epi	1.0	1.0	31.0	32.0	2.2	1.4	No	Alive, CRT terminated
Functionally single ventricle																
29	23.6	6.6	DILV	TCPC	TVP	0	No	Epi	2.0	3.0	34.8	22.8	7.8	6.2	No	Alive
30	14.5	12.2	DILV	TCPC	0	0	Yes	Epi	3.0	3.0	15.2	18.5	17.8	11.8	No	Alive
31	3.7	1.1	HLH	TCPC, TVP	0	0	No	Epi	3.0	2.0	29.4	40.0	8.7	6.6	Yes	SCD
32	2.1	5.4	HLH	BCPA, TVR	0	TCPC	No	Epi	2.0	2.0	16.1	28.7	5.1	1.9	Yes	Alive

AS indicates aortic stenosis; ASD, atrial septal defect; AVR, aortic valve replacement; AVSD-C, complete atrioventricular septal defect; AVSD-I, incomplete atrioventricular septal defect; BCPA, bidirectional cavopulmonary anastomosis; BE, bacterial endocarditis; CCAVB, congenital complete atrioventricular block; CND, pulmonary conduit replacement; CRT, cardiac resynchronization therapy; CTGA, congenitally corrected transposition of great arteries; COA, coarctation of the aorta; COR, correction; COR (sRV), correction with systemic right ventricle; dePAB, debanding; DILV, double-inlet left ventricle; DORV, double-outlet right ventricle; EDDz, systemic ventricular end-diastolic dimension(z-score); EF, ejection fraction; Epi, epicardial; FAC, fractional area of change; FUP, follow up; HLH, hypoplastic left heart syndrome; impl., implantation; LV, left ventricle; MR, mitral regurgitation; MS, mitral stenosis; Mustard, Mustard procedure; MVR, mitral valve replacement; NYHA, New York Heart Association functional class; PAB, pulmonary artery banding; PA/IVS, pulmonary atresia with intact ventricular septum; Pat. No, patient number; PA/VSD, pulmonary atresia with ventricular septal defect; PS, pulmonary stenosis; PVR, pulmonary valve replacement; Ross, Ross procedure; RV, right ventricle; SCD, sudden cardiac death; Senning, Senning procedure; SV, functionally single ventricle; TCPC, total cavopulmonary connection; TGA, transposition of great arteries; TV, transvenous; TVP, tricuspid valve plasty; TVR, tricuspid valve replacement; VI, ventricular inversion; VSD, ventricular septal defect; yrs, year