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ORIGINAL RESEARCH

Cardiac Resynchronization Therapy for Adult Patients With a Failing Systemic Right Ventricle: A Multicenter Study

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BACKGROUND: The objective of this international multicenter study was to investigate both early and late outcomes of cardiac resynchronization therapy (CRT) in patients with a systemic right ventricle (SRV) and to identify predictors for congestive heart failure readmissions and mortality.

METHODS AND RESULTS: This retrospective international multicenter study included 13 centers. The study population comprised 80 adult patients with SRV (48.9% women) with a mean age of 45±14 (range, 18–77) years at initiation of CRT. Median follow-up time was 4.1 (25th–75th percentile, 1.3–8.3) years. Underlying congenital heart disease consisted of congenitally corrected transposition of the great arteries and dextro-transposition of the great arteries in 63 (78.8%) and 17 (21.3%) patients, respectively. CRT resulted in significant improvement in functional class (before CRT: III, 25th–75th percentile, II–III; after CRT: II, 25th–75th percentile, II–III; P=0.005) and QRS duration (before CRT: 176±27; after CRT: 150±24 milliseconds; P=0.003) in patients with pre-CRT ventricular pacing who underwent an upgrade to a CRT device (n=49). These improvements persisted during long-term follow-up with a marginal but significant increase in SRV function (before CRT; 30%, 25th–75th percentile, 25–35; after CRT: 31%, 25th–75th percentile, 21–38; P=0.049). In contrast, no beneficial change in the above-mentioned variables was observed in patients who underwent de novo CRT (n=31). A quarter of all patients were readmitted for heart failure during follow-up, and mortality at latest follow-up was 21.3%.

CONCLUSIONS: This international experience with CRT in patients with an SRV demonstrated that CRT in selected patients with SRV dysfunction and pacing-induced dyssynchrony yielded consistent improvement in QRS duration and New York Heart Association functional status, with a marginal increase in SRV function.

Key Words: cardiac resynchronization therapy ■ congenital heart disease ■ heart failure ■ pacing ■ systemic right ventricle

Heart failure is a major source of morbidity and the leading cause of mortality in adults with congenital heart disease (CHD).[1,2] As a consequence of advances in surgical techniques and catheter-based interventions, life span has increased, resulting in a higher incidence of congestive heart failure in this challenging population. Cardiac resynchronization therapy (CRT) is a potential treatment modality for selected patients with CHD with progressive congestive heart failure. In addition to optimal medical therapy, CRT carries the

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CLINICAL PERSPECTIVE

What Is New?

- This is the largest multicenter experience with cardiac resynchronization therapy (CRT) in adult patients with a systemic right ventricle demonstrating that CRT resulted in significant improvement in functional class and decrease in QRS duration in patients with pre-CRT ventricular pacing.
- In contrast, no beneficial change in the above-mentioned variables was observed in patients who underwent de novo CRT.

What Are the Clinical Implications?

- Upgrade to CRT should be strongly considered in patients with ventricular pacing waiting for cardiac transplantation.
- CRT can be a potentially important treatment option for patients with systemic right ventricle without prior ventricular pacing who require ventricular pacing.
- Future studies are warranted to determine whether CRT is superior compared with optimal medical therapy or subpulmonary left ventricular pacing alone.

Nonstandard Abbreviations and Acronyms

CCTGA	congenitally corrected transposition of the great arteries
CRT	cardiac resynchronization therapy
D-TGA	dextro-transposition of the great arteries
NYHA	New York Heart Association
QRSd	QRS duration
SRV	systemic right ventricle

potential to improve survival and quality of life. However, supporting evidence in favor of CRT in patients with CHD is limited, prompting cautious evidence-based recommendations.[1,2]

In the most recent guidelines for management of adults with CHD, the exact role of CRT in this heterogeneous population was identified as one of the major knowledge gaps, especially since long-term data are lacking.[1] This is particularly applicable to patients with a systemic right ventricle (SRV). An SRV differs from a systemic left ventricle in terms of embryological origin, anatomy, and functional and electrophysiological properties.[3,4] As such, recommendations for CRT pertaining to a systemic left ventricle should not be extrapolated to an SRV.

A recently published review on CRT in patients with an SRV concluded that large studies reporting on both short- and long-term outcome are indeed lacking but neccesary.[5] There are no uniform selection criteria or predefined measures to examine the efficacy of CRT. In the largest study—consisting of only 36 patients with SRV—a nonresponder rate of 14% was reported. Limitations of that study included that both pediatric and adult patients were included, patient-specific data were not described, and follow-up was limited to 6 months.[6] The objective of this international multicenter study was to investigate both early and late outcomes of CRT in patients with an SRV and to identify predictors for congestive heart failure readmissions and mortality.

METHODS

The data underlying this article will be shared on reasonable request to the corresponding author.

This retrospective cohort study was initiated by the joint Pediatric and Congenital Electrophysiology Society/International Society of Adult Congenital Heart Disease Electrophysiology Research Working Group and included 13 centers in the United States, Canada, and Europe (Figure S1). Institutional review board approval was obtained at each site, and the informed consent was waived. Data were transferred to the coordinating center at Erasmus Medical Center through Research Electronic Data Capture. All adults with either congenitally corrected transposition of the great arteries (CCTGA) or dextro-transposition of the great arteries (D-TGA) with previous atrial switch repair (Mustard or Senning procedure) were included for analysis. Patients aged younger than 18 years at the time of CRT implantation and patients with univentricular hearts were excluded from analysis. Patients who were followed at another center were also excluded.

Baseline Characteristics and CRT Procedural Data

Data were retrieved from medical records and included demographic variables, underlying heart disease, history of surgical of interventions, pharmacologic therapy, New York Heart Association (NYHA) functional class, echo- and electrocardiographic parameters and Holter monitoring reports. Intra- and early postprocedural data included CRT approach (transvenous or epicardial), type of CRT device (CRT- defibrillator or CRT- pacemaker), and SRV lead position (outflow tract, basal-, mid- or apical-segments). Data on early (≤30 days) postprocedural complications (lead dislocation, pocket infection/hematoma, cardiac tamponade, hemothorax, pneumothorax, stroke, and mortality) were also collected.

Electrocardiographic Data

Pre-CRT, short-term (≤6 months after CRT) and long-term (at last follow-up) electrocardiographic data were collected for all patients to determine QRS duration (QRSd). History of atrial fibrillation (AF), atrial flutter, or other supraventricular tachycardia was also documented.

Echocardiographic Data

Echocardiographic data were retrieved from pre-CRT short- and long-term echocardiographic assessments, including qualitative systemic and nonsystemic ventricular function (normal; mildly, moderately, or severely impaired) and ejection fraction (EF).

Follow-Up Data

Follow-up data were gathered from outpatient clinic visits. During short- and long-term follow-up, echocardiographic and electrocardiographic parameters and NYHA functional class were retrieved from medical records. As there is variability in the literature regarding the definition of "nonresponders," outcomes were reported separately for 3 variables of interest: QRSd, EF, and NYHA class.

Statistical Analysis

Normality was assessed using the Kolmogorov–Smirnov test. Baseline characteristics are reported as mean±SD for normally distributed continuous variables and median with 25th to 75th percentile or range for skewed data. Differences in means and medians were calculated using the Student *t*-test, Mann–Whitney *U* test, or Kruskal-Wallis test. Categorical data are presented as numbers and percentages and compared with the chi-squared test or the Fisher exact test as appropriate. Comparison of continuous variables within a patient were performed using the paired Student *t* test or Wilcoxon signed-rank test. Survival after CRT implantation was assessed by Kaplan–Meier Survival Analysis. Univariate Cox regression analysis was performed to determine factors associated with readmission and mortality. Hazard ratios (HRs) are reported with 95% CIs. A *P* value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY).

RESULTS

Study Population

Baseline characteristics are summarized in Table 1. The study population comprised 80 patients with an SRV (48.9% women) with a mean age of 45±14 (range, 18–77) years at initiation of CRT. Median follow-up time was 4.1 (range, 1.3–8.3) years. Underlying CHD consisted of congenitally CCTGA and D-TGA in 63 (78.8%) and 17 (21.3%) patients, respectively. Only 10% of the patients were diagnosed with AF or atrial flutter (Table 1). Twenty-four (38.1%) patients with CCTGA had a history of at least 1 cardiac surgical procedure.

Forty-nine (61.3%) patients had ventricular pacing-induced (>40% pacing) cardiomyopathy (median time to CRT upgrade, 11.8 years; range, 4.0–21.6), 8 (10.0%) had complete atrioventricular conduction block, 11 (13.8%) had heart failure with a bundle branch block, and 1 (1.3%) had ischemic cardiomyopathy. The exact indication for CRT could not be retrieved from patient records in the remaining 11 (13.8%) patients. Mean QRSd was 161±36 milliseconds (range, 82–240), and 31 (38.8%) patients were in NYHA class III/IV. Systemic and nonsystemic ventricular function was moderately or severely impaired in 83% and 15%, respectively, with a median systemic ventricular EF of 30% (range, 25%–39%). Preoperative usage of diuretics, angiotensin-converting enzyme inhibitors and antiarrhythmic drugs are summarized in Table 1.

CRT Systems

The time period over which CRT implantation procedures were performed is 2003–2020. Fifty-six (70.0%) patients received a CRT-defibrillator device, whereas 24 (30.0%) received a CRT-pacemaker. CRT leads were implanted exclusively by a transvenous approach in 52 (65.0%) patients, epicardially in 10 (12.5%), and via a mixed approach in 18 (22.5%). In most patients (n=69; 86.3%), the nonsystemic ventricular lead was implanted transvenously, whereas the SRV lead was implanted transvenously in 53 (66.3%) patients. SRV lead position (available in 78 [97.5%] patients) was near the outflow tract in 6 (7.7%), basal segment in 21 (26.9%), mid segments in 35 (44.9%), and near the apex in 16 (20.5%). Early postprocedural complications consisted of lead dislodgement (n=3), pocket infection or hematoma (n=3), cardiac tamponade (n=1), and pneumothorax (n=3).

Short-Term Outcomes

Data on short-term outcomes (≤6 months) of CRT were available in 74 patients (93%). Eighteen (22.5%) of the patients were in NYHA class III/IV within 6 months after CRT. Patients with ventricular pacing before CRT showed a significant decrease in QRSd (before CRT: 176±27 milliseconds; after CRT: 150±24 milliseconds, *P*=0.003) and improvement in NYHA class (before CRT: III, II–III; after CRT: II, II–III; *P*=0.005). Median time to short-term echocardiographic evaluation was 3 months (range, 1–6 months). In patients without ventricular pacing before CRT, there was prolongation in

Table 1. Baseline Characteristics

	Total N=80	CCTGA N=63	D-TGA N=17	*P* value	Pre-CRT ventricular pacing N=49	No pacing before CRT N=31	*P* value
Age, y	45.4±13.7	47.6±14.2	37.3±7.9	0.005	45.1±13.6	46.0±14.2	0.763
Sex, female	38 (47.5%)	30	8	0.967	28	10	0.030
Diabetes	12 (15%)	9	3	0.711	9	3	0.289
Hypertension	25 (31.3%)	20	5	0.854	15	10	0.877
Hypercholesterolemia	14 (17.5%)	13	1	0.280	7	7	0.341
Coronary artery disease	14 (17.5%)	10	4	0.482	7	7	0.341
Severe kidney failure (eGFR ≤30)	12 (15%)	9	3	0.711	7	5	0.822
Electrocardiographic data							
QRSd, ms	161±36	158±34	169±44	0.386	176±27	137±36	<0.001
RBBB	4 (5%)	4	0			3	
LBBB	2 (2.5%)	2	0			2	
IVCD	2 (2.5%)	2	0			2	
History of AF/atrial flutter	8	5	3	0.192	7	1	0.108
Paroxysmal AF	0	0	0		0	0	
Nonparoxysmal AF	5 (6.3%)	2	3		4	1	
Atrial flutter	3 (3.8%)	3	0		3	0	
Pre-CRT ventricular pacing	49 (61.3%)	37	12	0.373	-	-	
NYHA functional class							
NYHA	3 (2–3)	3 (2–3)	3 (2–3)	0.508	3 (2–3)	3 (2–3)	0.576
I	4 (5%)	3	1		1	3	
II	15 (18.8%)	13	2		11	4	
III	27 (33.8%)	20	7		17	10	
IV	4 (5%)	3	1		3	1	
Ejection fraction, %	30 (25–39)	30 (25–39)	28 (25–38)	0.822	30 (25–34)	35 (25–45)	0.330
SV dilatation	35 (43.8%)	31	4	0.682	21	14	0.368
Diuretics	63 (78.8%)	49	14	0.849	40	23	0.428
ACE-i	64 (80%)	53	11	0.076	41	23	0.302
Digoxin	30 (37.5%)	25	5	0.438	21	9	0.213
Antiarrhythmic drugs class							
I	4 (5%)	3	1	0.851	4	0	0.103
II (including beta blockers)	37 (46.3%)	27	10	0.241	25	12	0.282
III	14 (17.5%)	8	6	0.030	9	5	0.797
IV	2 (2.5%)	2	0	0.457	2	0	0.255

ACE-i indicates angiotensin-converting enzyme-inhibitor; AF, atrial fibrillation; CCTGA, congenitally corrected transposition of the great arteries; CRT, cardiac resynchronization therapy; D-TGA, dextro-transposition of the great arteries; e-GFR, estimated glomerular filtration rate; IVCD, intraventricular conduction delay; LBBB, left bundle branch block; NYHA, New York Heart Association; QRSd, QRS duration; RBBB, right bundle-branch block; and SV, systemic ventricle.

QRSd (before CRT: 137±36 milliseconds; after CRT: 154±25 milliseconds; *P*=0.016) but improvement in NYHA class (before CRT: III, II–III; after CRT: II, I–III; *P*=0.015). However, there was no improvement in EF in both groups (*P*>0.078).

Long-Term Outcomes

Long-term data (>6 months) were available in 90% of the patients. After a median follow-up of 4.1 (range, 1.3–8.3) years, patients with pre-CRT ventricular pacing who were upgraded to CRT showed significant reduction in QRSd (156±28 milliseconds versus 176±27 milliseconds; *P*=0.002), improvement in NYHA class (II, II–III versus III, II–III; *P*=0.001) and a marginal increase in EF (31%, 21%–38% versus 30%, 25–34; *P*=0.049) compared with baseline. In contrast, patients without ventricular pacing before CRT had no improvement in EF (35%, 19%–40% versus 35%, 25–45; *P*=0.458) or NYHA class (II, I–III versus III, II–III; *P*=0.087), and had a significant increase in QRSd (137±36 milliseconds versus 150±43 milliseconds;

P=0.023). At latest follow-up, 46% of the patients were in NYHA class III/IV. Two events of lead dislodgement were reported during follow-up. More detailed data on changes in NYHA class are provided in Table S1.

CCTGA Versus D-TGA

As summarized in Table 1, patients with CCTGA were older at baseline compared with those with D-TGA (48±14 versus 37±8 years; *P*=0.005) and had similar follow-up duration (*P*=0.930). No baseline differences were observed between groups with respect to QRSd, EF, or NYHA class (all *P*>0.386). A complete transvenous CRT system was implanted in 79% of the patients with CCTGA and 12% of the patients with D-TGA. As shown in Table 2, during both short- and long-term follow-up, NYHA class and EF did not differ significantly between groups, except for short-term QRSd. Acutely, patients with D-TGA had a shorter QRSd compared with patients with CCTGA (130±21 versus 155±23 milliseconds; *P*=0.005) but this was no longer significant at last follow-up (148±37 versus 157±34 milliseconds; *P*=0.417).

Transvenous Versus Epicardial or Mixed CRT Systems

Differences in baseline and short- and long-term outcomes between patients with a completely transvenous system and patients with at least 1 epicardial lead are summarized in Table S2. There were no significant differences in EF, QRSd, and NYHA class between both groups (all *P*>0.151).

Hospital Readmission

During follow-up, 21 (26%) patients were readmitted for congestive heart failure with a median time to rehospitalization of 1.1 (range, 0.2–5.9) years. Presence of diabetes (HR=3.06 [95% CI, 1.15–8.16]; *P*=0.025) and hypertension (HR=2.44 [95% CI, 1.03–5.77]; *P*=0.043) at baseline were significantly associated with readmission for congestive heart failure (Table 3). In addition, patients in whom no improvement was observed in NYHA class also had an ≈5-fold higher risk of being readmitted for heart failure (HR=5.18 [95% CI, 1.07–25.05]; *P*=0.041). Patients with an SRV lead in basal segments had a higher risk for readmission for heart failure (HR=3.23 [95% CI, 1.30–8.01]; *P*=0.011). No significant associations were observed for the other locations. During follow-up, 10 patients were listed for heart transplantation and all of them survived the waiting period. At the time of analysis, 6 patients received their transplantation at a median of 4.8 years (earliest and latest time to transplantation was 2.3 and 9.0 years, respectively) after CRT.

Mortality

Mortality at 5 years of follow-up was 7.5% and increased to 21.3% at latest follow-up. As shown in Figure 1, survival did not differ between patients with CCTGA and patients with D-TGA following CRT (*P*=0.548), and not between patients with pre-CRT ventricular pacing and no pre-CRT ventricular pacing (*P*=0.453). Cause of death could be retrieved in 10 (59%) patients and consisted of progressive heart failure (n=5), hemodynamic and respiratory failure after

Table 2. Short- and Long-Term Outcome

	Baseline	6 mo after CRT	*P* value	Latest follow-up	*P* value
CCTGA, N=63					
EF, %	30 (25–39)	33 (29–41)	0.04	35 (25–40)	0.62
QRSd, ms	158±34	155±23	0.83	157±34	0.06
NYHA	3 (2–3)	2 (1–3)	<0.01	2 (2–3)	0.40
D-TGA, N=17					
EF, %	28 (25–38)	28 (21–41)	1.00	20 (10–37)	0.11
QRSd, ms	169±44	130±21	0.05	148±37	0.49
NYHA	3 (2–3)	2.5 (1–3)	0.16	3 (1–4)	0.92
Pre-CRT ventricular pacing, N=49					
EF, %	30 (25–34)	30 (30–45)	0.08	31 (21–38)	0.33
QRSd, ms	176±27	150±24	<0.01	156±28	0.07
NYHA	3 (2–3)	2 (2–3)	<0.01	2 (2–3)	0.71
No pacing before CRT, N=31					
EF, %	35 (25–45)	33 (17–37)	0.28	35 (19–40)	0.47
QRSd, ms	137±36	154±25	0.02	153±43	0.85
NYHA	3 (2–3)	2 (1–3)	0.02	2 (1–3)	0.45

CCTGA indicates congenitally corrected transposition of the great arteries; CRT, cardiac resynchronization therapy; D-TGA, dextro-transposition of the great arteries; EF, ejection fraction; NYHA, New York Heart Association; and QRSd, QRS duration.

Table 3. Factors Associated With Readmission for Congestive Heart Failure

Determinant	Univariate analysis, HR (95% CI)	*P* value
Sex, male	1.40 (0.57–3.45)	0.46
Age, y	1.02 (0.99–1.05)	0.21
CCTGA	0.71 (0.27–1.84)	0.48
CAD	1.67 (0.66–4.23)	0.28
Type 2 diabetes	3.06 (1.15–8.16)	0.03
Hypertension	2.44 (1.03–5.77)	0.04
Hypercholesterolemia	2.23 (0.84–5.95)	0.11
Pre-CRT ventricular pacing	0.67 (0.33–2.02)	0.67
QRS >140 ms	1.40 (0.38–5.15)	0.61
NYHA III/IV	1.42 (0.36–5.52)	0.62
M/S SRV function	2.81 (0.36–22.29)	0.33
No decrease QRS	0.62 (0.19–2.08)	0.44
No improvement in NYHA	5.18 (1.07–25.05)	0.04
SRV lead—RVOT	1.62 (0.37–7.20)	0.52
SRV lead—basal	3.23 (1.30–8.01)	0.01
SRV lead—mid	0.56 (0.20–1.58)	0.27
SRV lead—apex	0.28 (0.06–1.23)	0.09

CAD indicates coronary artery disease; CCTGA, congenitally corrected transposition of the great arteries; CRT, cardiac resynchronization therapy; HR, hazard ratio; M/S, moderately/severely impaired; NYHA, New York Heart Association; RVOT, right ventricular outflow tract; and SRV, systemic right ventricle.

heart transplantation (n=2), sudden cardiac death with CRT- defibrillator device failure (n=1), postpartum cardiomyopathy with multiorgan failure (n=1), and cerebrovascular accident. As summarized in Table 4, no predictors for mortality could be identified (all *P*>0.077).

DISCUSSION

Key findings from this multicenter experience with CRT in adult patients with CHD with an SRV are that CRT resulted in significant improvement in functional class and decrease in QRSd in patients with pre-CRT ventricular pacing who underwent an upgrade to a CRT device. These improvements persisted during long-term follow-up (median follow-up time, 4.1 years). In contrast, no beneficial change in the above-mentioned variables was observed in patients who underwent de novo CRT. With the exception of age, there were no relevant differences in baseline characteristics between patients with CCTGA versus patients with D-TGA and atrial switch surgery. A quarter of all patients were readmitted for heart failure during follow-up. At latest follow-up (median, 4.1 years), mortality was 21.3% (Figure 2). Our data support the use of CRT in patients with an SRV and preexisting ventricular pacing. However, our data do not substantiate primary CRT in patients without prior ventricular pacing.

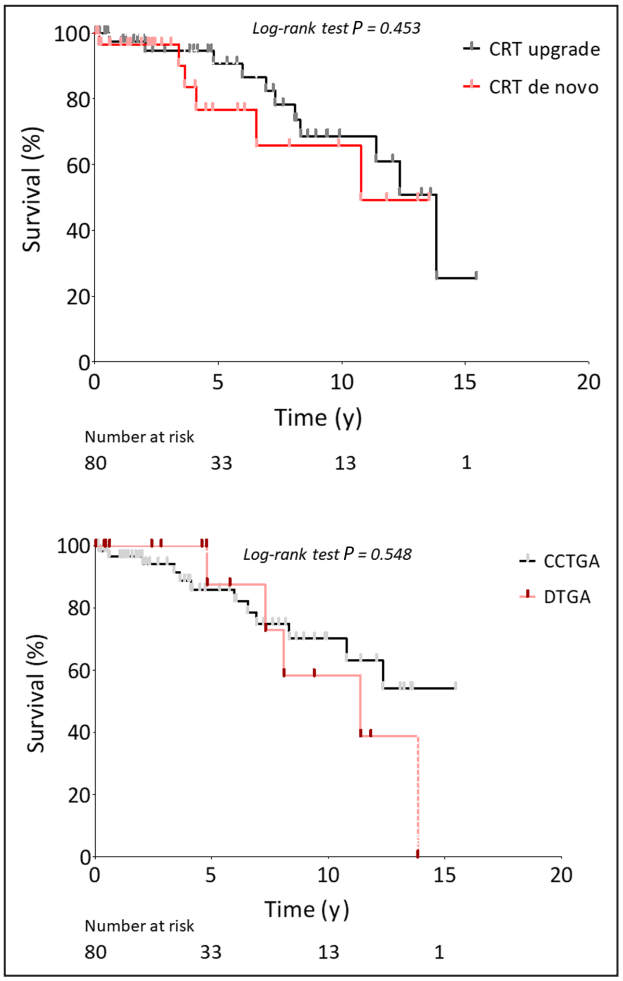

Figure 1. Kaplan–Meier curves comparable long-term survival of patients with pre-CRT ventricular pacing (CRT upgrade) and patients without ventricular pacing before CRT (CRT de novo) (upper panel) and Kaplan–Meier curves depicting comparable long-term survival of patients with CCTGA or DTGA (lower panel).
CCTGA indicates congenitally corrected transposition of the great arteries; CRT, cardiac resynchronization therapy; and D-TGA, dextro-transposition of the great arteries.

Multicenter Experience of CRT in Patients With SRV

Multiple small studies demonstrated encouraging outcomes of CRT for patients with SRV (pediatric and adult patients); however, long-term data and large study cohorts remain lacking.[7–11] The 2 largest multicenter studies to date performed by Dubin et al[11] and Janousek et al[6] included 17 and 27 patients with SRV, respectively. Both studies reported beneficial acute responses to CRT, including improvement in functional status, SRV, and EF and decrease in QRSd. However, the study populations consisted of pediatric and adult patients with different underlying heart diseases, and long-term outcomes were not assessed. In addition, Dubin et al[11] defined "nonresponders" as patients with

Table 4. Predictors for Mortality

Determinant	Univariate analysis HR (95% CI)	*P* value
Sex, male	1.95 (0.67–5.65)	0.22
Age, y	1.03 (1.00–1.07)	0.08
CCTGA	0.72 (0.25–2.09)	0.55
CAD	1.22 (0.42–3.60)	0.72
Type 2 diabetes	0.52 (0.07–4.00)	0.53
Hypertension	1.82 (0.70–4.74)	0.22
Hypercholesterolemia	0.77 (0.17–3.44)	0.73
Pre-CRT ventricular pacing	0.68 (0.24–1.88)	0.46
QRS >140 ms	2.40 (0.30–19.08)	0.41
NYHA III/IV	0.86 (0.19–3.84)	0.84
M/S SRV function	0.80 (0.10–6.54)	0.83
Readmission HF	2.21 (0.84–5.77)	0.11
No decrease in QRS	0.95 (0.24–3.79)	0.94
No improvement in NYHA	3.20 (0.57–17.84)	0.18
SRV lead—RVOT	1.10 (0.14–8.47)	0.93
SRV lead—basal	1.71 (0.63–4.64)	0.29
SRV lead—mid	1.20 (0.42–3.45)	0.73
SRV lead—apex	0.34 (0.08–1.51)	0.16

CAD indicates coronary artery disease; CCTGA, congenitally corrected transposition of the great arteries; CRT, cardiac resynchronization therapy; HF, heart failure; HT, hypertension; HR, hazard ratio; M/S, moderately/severely impaired; NYHA, New York Heart Association; RVOT, right ventricular outflow tract; and SRV, systemic right ventricle.

either no change or deterioration in SRV function, while Janousek et al[6] defined "nonresponders" as patients with either no change or deterioration in SRV function *and* no clinical response defined as a decrease in NYHA class.[6,11] A recent study including 20 adults with CCTGA reported sustained improvements in NYHA functional class by ≥1 class or ≥10% increase in fractional area change in 67% of patients (median follow-up, 4.6 years).[12] Our findings confirm these preliminary outcomes and further substantiate an important role for CRT in patients with CCTGA and patients with D-TGA. In addition, we report a generally favorable long-term clinical course with low readmission rates for heart failure and good survival. Notably, the prevalence of AF/atrial flutter was lower in our cohort compared with previous studies,[13] which might have an influence on the favorable long-term outcomes. This might be a result of selection bias, underreporting, or coincidence.

Upgrade or De Novo CRT Implantation

At present, there are no large studies comparing differences in outcome between patients with preexisting ventricular pacing undergoing an upgrade and patients receiving CRT de novo. Moore et al[12] observed a trend toward less favorable acute outcomes in patients without pre-CRT ventricular pacing who underwent CRT with the indication of complete atrioventricular

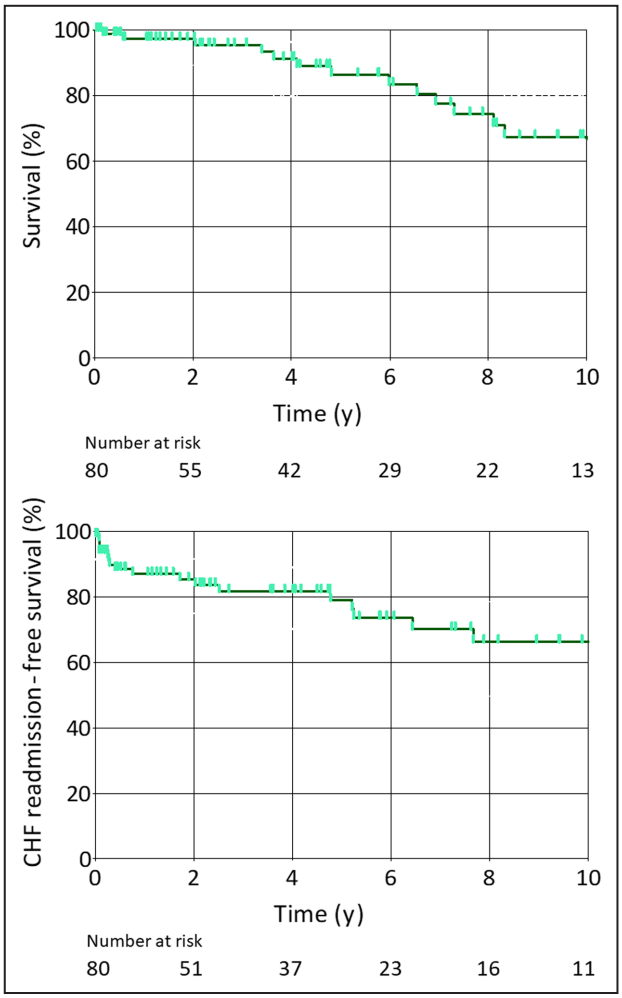

Figure 2. Kaplan–Meier curve depicting overall survival in 80 patients with a systemic right ventricle (upper panel) and Kaplan–Meier curve depicting the CHF readmission-free survival for all patients (lower panel).
CHF indicates congestive heart failure.

conduction block. These patients often present with a narrow complex junctional rhythm. Our findings confirm that these patients have less improvement in SRV function and also have a more prolonged QRSd. However, as previously described in CRT studies, placebo effects are powerful and may be reflected by subjective improvements in NYHA class, as observed in our study. At latest follow-up, these patients remained stable with NYHA class (II, I–III), EF (35%; 19–40) and QRSd (153±43 milliseconds). Although we did not observe clinical deterioration in this subgroup, future studies are warranted to determine whether CRT or novel emerging therapies, such as His bundle or left bundle branch pacing, may ultimately improve clinical outcomes compared with subpulmonary left ventricular (LV) pacing alone.[14] A randomized controlled trial of CRT versus subpulmonary LV pacing in patients requiring pacemaker therapy would also be of great clinical value.

SVR Lead Location: Does It Matter or Not?

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study was the first randomized controlled trial analyzing the effect of LV lead position on outcomes in a non-CHD cohort (n=799).[15] Patients with apical position of the LV lead showed an increased risk for heart failure or death (HR, 1.72 [95% CI, 1.09–2.71]; *P*=0.019) compared with patients with a lead in the other regions (anterior, lateral, or posterior left ventricle). Extensive research in experimental and computational models followed and demonstrated that optimal systemic LV lead placement is crucial to maximize ventricular synchrony and clinical outcomes.[16–18] Despite emerging evidence on the influence of LV lead position on clinical outcomes, the ideal approach for optimal lead position for the SRV population remains unexplored.[7,9,19] Miyazaki et al[19] suggested that the most effective lead positions in this population are the right ventricular outflow tract and basal segments, which often correspond to sites of latest activation. Indeed, Moore et al[7] demonstrated by performing endocardial and epicardial electroanatomical mapping in patients with an SRV during a hybrid CRT implantation approach that the latest sites of activation were often the basolateral and right ventricular outflow tract segments.

Surprisingly, in the present study, patients with SRV leads at basal segments had a higher risk for readmission for heart failure (HR=3.231 [95% CI, 1.303–8.009] *P*=0.011), with no effect on survival (HR=1.709 [95% CI, 0.630–4.640]; *P*=0.293). Point estimates for heart failure readmission rates in patients with SRV leads in the apex were numerically lower but not significantly so (HR=0.281 [95% CI, 0.064–1.232]; *P*=0.092). Similar findings were recently observed by Leyva et al[20] who investigated 1189 patients with (non)ischemic cardiomyopathy undergoing CRT. Apical left ventricular lead position was associated with a lower risk of heart failure than a nonapical left ventricular lead position. In addition, in patients with ischemic cardiomyopathy, this also led to better survival.

Unfortunately, contraction patterns and adaptation mechanisms of the SRV are largely unknown. However, it is conceivable that apical pacing in a failing SRV may improve its electromechanical coupling. Also, circumferential rather than longitudinal shortening is a characteristic of an SRV with chronic pressure overload.[21] If further studies demonstrate that apical pacing is superior to other sites, it could be hypothesized that it is a result of improvement in longitudinal shortening. If not, the relatively low sample size of our study might have resulted in a false association.

Recent survival data show a 5-year survival rate of ≈80% for adult patients with CHD undergoing CRT.[22,23] The 5-year survival rate in the present study is 85%, which is in line with a recent single-center study including 31 patients with SRV.[24] Our data indicate that CRT, regardless of precise lead location, is a promising long-term therapy in patients with SRV with ventricular pacing–induced dyssynchrony. However, to determine the effect of lead location on outcomes, future prospective studies are required, with a focus on lead positioning, such as by electroanatomical mapping guidance.

Limitations

This study has several limitations inherent to its retrospective study design. As the level of evidence of recent guidelines is limited, patients underwent CRT according to local preferences and practices. Echocardiographic assessment of EF for an SRV is not the most accurate tool to determine SRV function. However, more advanced imaging modalities to examine ventricular function, other than echocardiography, were lacking, and functional assessment was limited to changes in NYHA class. This study included patients treated over a 20-year period and therefore advanced intraprocedural data, measures of ventricular dyssynchrony, and periodic rhythm and echocardiographic monitoring were not routinely available. Data on medical therapy were scarcely available and were therefore not included in the analysis. There were insufficient data on nonsystemic ventricular lead location, interlead distance, and CRT optimization for analysis. Although this is the largest study in this field, subanalyses on specific patient groups (eg, de novo CRT group) may be underpowered, possibly resulting in nonsignificant outcomes. Despite these limitations, the study outcomes provide novel insights into outcomes of CRT in a complex and rare population of patients in whom heart failure is highly prevalent. Future prospective multicenter registries and randomized controlled trials are required to precisely determine selection criteria and identify patients who are most likely to derive long-term benefit from CRT.

CONCLUSIONS

This multicenter experience with CRT in 80 patients with SRV demonstrated that CRT in selected patients with SRV dysfunction and pacing-induced dyssynchrony yielded consistent improvement (median follow-up time, 4.1 years) in QRSd and NYHA functional status, with a minimal increase in EF, which is most likely clinically irrelevant. Therefore, upgrade to CRT should be strongly considered in patients with ventricular pacing waiting for cardiac transplantation. Beneficial effects in patients without pre-CRT ventricular pacing were

less marked. Underlying reasons remain to be determined but may be attributable, in part, to the narrower preprocedural QRSd and better functional class observed in this subgroup of patients. Over a period of 5 years, SRV function and functional status remained stable in these patients. Future studies are warranted to determine whether CRT is superior compared with optimal medical therapy or subpulmonary LV pacing alone. Subgroup analysis revealed no relevant differences in outcomes between patients with CCTG and patients with D-TGA, and between patients with only transvenous leads and mixed or epicardial systems.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2
Figure S1

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Supplemental Material

Table S1. Change in New York Heart Association (NYHA) functional class after cardiac resynchronization therapy.

	Pre-CRT, n=	**Short-term (<6m), n=**	**Long-term (>6m), n=**
NYHA I	4 (8%)	15 (28%)	21 (26.5%)
NYHA II	25 (50%)	20 (38%)	21 (26.5%)
NYHA II	17 (34%)	14 (26%)	23 (29%)
NYHA IV	4 (8%)	4 (8%)	14 (18%)

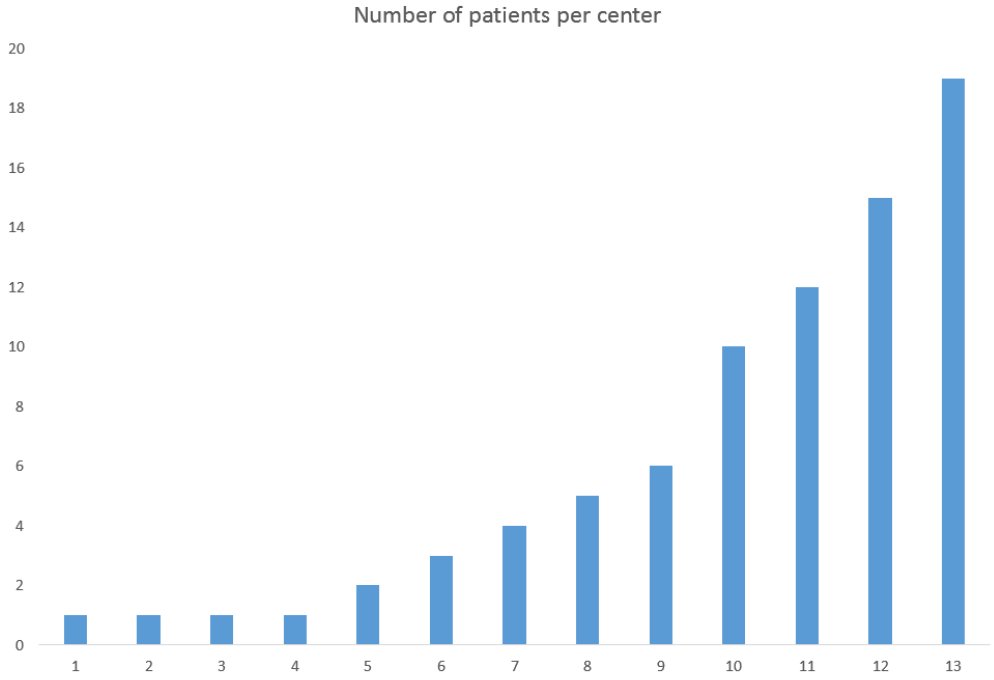
CRT= Cardiac resynchronization therapy, m= months, NYHA= New York Heart Association

Table S2. Differences in baseline, short- and long-term outcomes between patients with a completely transvenous system and patients with at least one epicardial lead.

	Baseline	6m post CRT	Latest FU
Transvenous CRT system N=52			
EF (%)	30 [25-35]	30 [29-35]	34 [24-36]
QRSd (ms)	161±33	153±25	156±32
NYHA	3 [2-3]	2 [1-3]	2 [2-3]
Epicardial/mixed CRT system N= 28			
EF	38 [25-47]	36 [21-45]	28 [17-40]
QRSd	160±43	147±23	152±39
NYHA	3 [2-3]	2 [1-3]	3 [1-3]

Same legend as Table 2

Figure S1. Participating institutions.



1. Children's Hospital of Philadelphia
2. University of Utah
3. University of Ottawa Heart Institute
4. San Francisco Medical Center
5. Aarhus University Hospital
6. Nationwide Children's Hospital
7. Erasmus Medical Center
8. University of Florida Health
9. Boston Children's Hospital
10. Stanford Medical University
11. Mayo Clinic Rochester
12. University of California Los Angeles
13. Emory University School of Medicine