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Cardiac resynchronization therapy in patients with congenital heart disease and systemic right ventricle

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BACKGROUND Although patients with systemic right ventricle (SRV) represent a significant proportion of patients with congenital heart disease (CHD) implanted with cardiac resynchronization therapy (CRT), there are limited and conflicting data in this specific patient group.

OBJECTIVE We aimed to analyze outcomes of patients with SRV implanted with a CRT device.

METHODS Data were analyzed from an observational, retrospective, multicenter cohort study including all patients with CHD implanted with a CRT device from 6 French centers from 2004 to 2020. *Response to CRT* was defined as an increase in systemic ventricular ejection fraction of $\geq 10\%$ and/or an improvement in New York Heart Association functional class by at least 1 grade.

RESULTS A total of 85 patients with CHD were enrolled (mean age 39.8 ± 20.0 years; 55 [64.7%] males; 25 defibrillators [29.4%]), including 31 patients with SRV (36.5%) (mean age 43.9 ± 19.8 years; 16 [51.6%] males). The mean change in QRS duration after

implantation was similar as compared with patients with systemic left ventricle (-46 ± 26 ms vs -35 ± 32 ms; $P = .16$). During a mean follow-up of 5.1 ± 3.5 years, late complications included 2 lead dysfunctions (6.5%), 3 CRT-related infections (9.7%), and 1 inappropriate implantable cardioverter-defibrillator shock (3.2%). The proportion of CRT responders at 6, 12, and 24 months were 82.6%, 80.0%, and 77.8% in patients with SRV vs 66.7%, 64.3%, and 69.6% in patients with systemic left ventricle ($P = \text{NS}$).

CONCLUSION In this multicenter cohort, one-third of patients with CHD implanted with a CRT device had SRV. CRT in patients with SRV was associated with a high rate of responders, comparable to that of patients with systemic left ventricle.

KEYWORDS Cardiac resynchronization therapy; Congenital heart disease; Systemic right ventricle; Transposition of the great arteries; Heart failure

Introduction

Heart failure is the leading cause of death in adult patients with congenital heart disease (CHD).¹ The number of affected patients is expected to continue to grow exponen-

tially because of the important increase and aging of this population.

Although cardiac resynchronization therapy (CRT) has been robustly shown to improve outcomes in symptomatic patients with heart failure and prolonged QRS duration (especially left bundle branch block),^{2,3} the level of evidence is much more limited in patients with CHD. Underlying phenotypes are various, including systemic right ventricles (SRVs), isolated subpulmonary right ventricle (RV) dysfunctions, and single ventricles, and most patients have a right bundle branch block pattern.⁴ All these specificities question the extrapolation of data reported in patients with acquired heart

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diseases. Only a few series have addressed the impact of CRT in patients with CHD, with heterogeneous populations.^{5–12} The paucity of specific data in patients with SRV^{13–18} has been highlighted as a major evidence gap and as a high-impact research question by the American Heart Association/American College of Cardiology guidelines committee.¹⁹

In the present article, we aimed to analyze outcomes of patients with SRV implanted with a CRT device and to evaluate the impact of CRT in SRV compared with other types of CHDs with systemic left ventricle.

Methods

Study settings

Data were analyzed from an observational, retrospective, multicenter cohort study including all patients with CHD implanted with a CRT device from 6 French centers from 2004 to 2020 ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04842851) identifier NCT04842851; a list of centers is provided

Study data were centralized, collected, and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the Cardiovascular Epidemiology Unit of the Paris Cardiovascular Research Center (Inserm 970, European Georges Pompidou Hospital, Paris, France).²⁰ This study complies to the French data protection committee (Commission Nationale Informatique et Liberté, CNIL, MR-004 n°2219047), was approved by the institutional review board, and adheres to Helsinki Declaration as revised in 2013.

Study population and data collected

CHD were classified according to the last American Heart Association/American College of Cardiology and European Society of Cardiology classifications.^{19,21} The group of patients with SRV included patients with D-transposition of the great arteries (D-TGA) with atrial switch operation (Mustard or Senning surgery) and patients with congenitally corrected transposition of the great arteries (cc-TGA) with SRV (excluding cc-TGA with systemic left ventricle postsurgical repair, eg, arterial switch procedure or Rastelli surgery).

Data collected included demographic characteristics, type of CHD, date and types of cardiac operations, comorbidities, comprehensive history of cardiac arrhythmias, indication and type of CRT device implanted, pharmacological therapy before CRT implantation, New York Heart Association (NYHA) classification, electrocardiographic and echocardiographic parameters. The lead placement was left at the discretion of the operator in the different centers, with the aim to maximize the distance between left ventricular (LV) and RV leads, but no systematic electrical mapping to optimize lead placement according to the RV-LV electrical delay was performed. Echocardiographic data were collected before CRT implantation and at different time points during follow-up of patients. The systemic ventricular ejection fraction was measured using the biplane Simpson's method.

Definitions and outcomes

Response to CRT was defined as an increase in systemic ventricular ejection fraction of $\geq 10\%$ and/or an improvement in NYHA class by at least 1 grade (in patients with baseline NYHA class \geq II). Outcomes were analyzed at 6, 12, and 24 months after CRT implantation. These time points were selected to assess the response to CRT at homogeneous intervals between patients with a standardized workup. Response to CRT was not evaluated in patients with concomitant cardiac surgery or structural intervention at the time of CRT implantation.

Other outcomes analyzed included CRT-related complications, heart transplantation, CRT deactivation, and vital status with cause of death (where appropriate). In patients who underwent cardiac surgery, structural intervention, heart transplantation, or CRT deactivation during follow-up, response to CRT was assessed only at time points before these events. Patients with heart transplantation or death from heart failure were considered as nonresponders.

Statistical analysis

Categorical data were reported as number and percentage. Continuous data were reported as mean \pm SD or median and interquartile range (IQR) for normally and nonnormally distributed data, respectively. Comparisons used the χ^2 test or Fisher exact test for categorical variables and the Student *t* test or Mann-Whitney-Wilcoxon test for continuous variables, as appropriate. Overall mortality and overall mortality or heart transplantation survival curves were plotted using the Kaplan-Meier method. Censoring occurred in the event of loss to follow-up. Log-rank tests were used to compare survivals between patients with SRV and patients with systemic left ventricle. Wilcoxon signed-rank tests and McNemar tests were used, respectively, to compare systemic ejection fraction and NYHA class changes at different time points with those at baseline. Univariate logistic regression models were used to identify factors associated with response to CRT. A 2-tailed *P* value of $< .05$ was considered statistically significant. All data were analyzed using R software, version 3.6.3 (R Project for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 85 patients with CHD implanted with a CRT device were enrolled (mean age 39.8 ± 20.0 years; 55 [64.7%] males), including 31 patients with SRV (36.5%) (Figure 1). Patient characteristics according to systemic ventricle status are presented in Table 1. At CRT implantation, most patients were in NYHA class II (42.4%) or III (50.6%) and only a minority in class I (7.1%). Main CRT indications were low systemic ejection fraction and wide QRS complex (16.5%) or low systemic ejection fraction and need for ventricular pacing (67.1%), whereas the CRT device was implanted in 14 patients with normal systemic ejection fraction and need for ventricular pacing (16.5%). The majority of patients ($n = 59$) had a cardiac device before CRT (upgrade, 69.4%). CRT devices

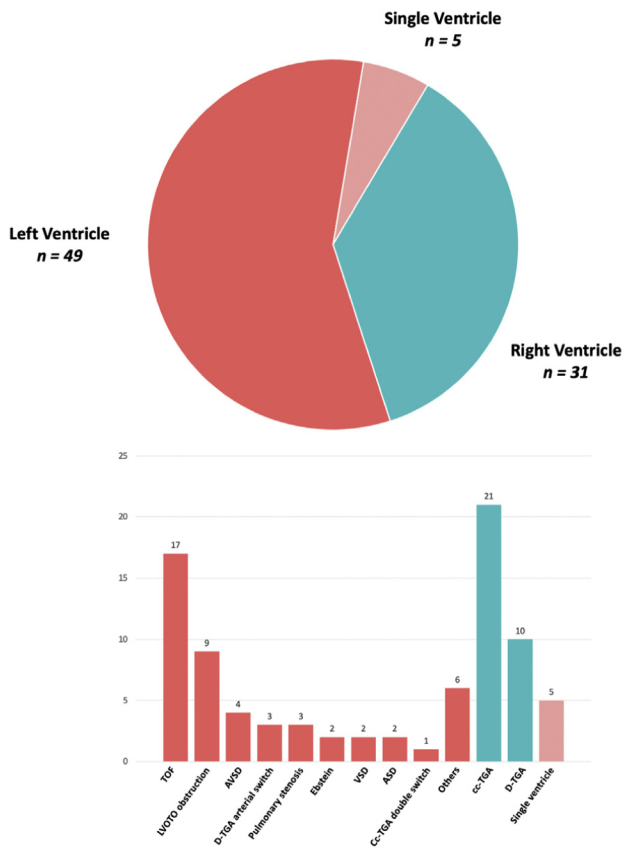


Figure 1 Congenital heart diseases included in the study. ASD = atrial septal defect; AVSD = atrioventricular septal defect; cc-TGA = congenitally corrected transposition of the great arteries; D-TGA = D-transposition of the great arteries; LVOTO = left ventricular outflow tract obstruction; TOF = tetralogy of Fallot; VSD = ventricular septal defect.

were endovascular in 39 patients (45.9%), epicardial in 35 (41.2%), and hybrid in 11 (12.9%; combination of endovascular and epicardial leads). Among all CRT devices, 25 (29.4%) were CRT-defibrillators including 6 (24.0%) implanted for secondary prevention. Among patients with SRV, 10 patients (32.3%) had a CRT-defibrillator including 1 (10.0%) for secondary prevention.

Compared with patients with systemic left ventricle, those with SRV had a lower median (IQR) number of cardiac surgeries (1 [0–1.5] vs 2 [1–3]; $P < .001$), a lower proportion of documented atrial arrhythmia (35.5% vs 61.2%; $P = .038$), and a lower median (IQR) systemic ejection fraction (35 [26.5–40] vs 40 [30–45]; $P = .022$) and were less frequently males (51.6% vs 73.5%, $P = .046$). Among 31 patients with SRV, the characteristics of patients with cc-TGA ($n = 21$) and patients with D-TGA and atrial switch operation ($n = 10$) are compared in [Table 2](#). Patients with D-TGA and atrial switch were younger than those with cc-TGA (33.0 ± 6.3 years vs 49.1 ± 21.9 years; $P = .004$), had a higher median (IQR) number of cardiac surgeries (1 [1–2] vs 0 [0–1]; $P = .020$), and more frequently had epicardial or hybrid CRT devices (100.0% epicardial or hybrid vs 42.9%; $P < .001$). Among the 12 patients with cc-TGA and an endovascular CRT device, coronary sinus abnormalities were reported in 2 (16.7%): one patient had a coronary sinus ostium

highly located arising from the superior right atrium near the right appendage and another patient had dual ostia (2 closely spaced coronary sinus ostia).

Device-related complications

Considering the whole cohort, the mean duration of follow-up after CRT implantation was 5.2 ± 3.8 years. During the early postoperative period (<30 days), 3 patients (3.5%) had acute CRT-related complications, namely, 2 pocket hematomas and 1 cardiac tamponade. Late complications included lead dysfunctions/fractures in 7 patients (8.2%), CRT-related infections in 4 (4.7%), and inappropriate implantable cardioverter-defibrillator (ICD) shock in 1 patient (1.2%) (lead fracture). All lead dysfunctions except one were related to epicardial leads and included 5 pacing leads (3 atrial and 2 ventricular leads) and 2 defibrillation coils.

Among patients with SRV, the only acute complication reported was 1 (3.2%) pocket hematoma and late complications included 2 lead dysfunctions/fractures (6.5%), 3 CRT-related infections (9.7%), and 1 inappropriate ICD shock (3.2%) over a mean follow-up of 5.1 ± 3.5 years. The proportion of patients experiencing acute (3.2% vs 2.0%; $P > .99$) and late (12.9% vs 10.2%; $P = .729$) CRT-related complications were similar in patients with SRV and in patients with systemic left ventricle.

Survival and heart transplantation

A total of 9 patients (10.6%) died, and 9 patients had heart transplantation (10.6%). Cardiogenic shock was the main cause of death ($n = 6$ including 3 after heart transplantation), 2 patients died of septic shock (1 endocarditis and 1 septic shock after heart transplantation), and the cause of death was unknown in 1 patient. Among patients with SRV, 3 died of cardiogenic shock (0.7%) ($n = 2$ including 1 after heart transplantation) and septic shock due to endocarditis ($n = 1$), and 5 (16.1%) had heart transplantation. Kaplan-Meier curves of survival free from overall mortality and overall mortality or heart transplantation in patients with SRV and in patients with systemic left ventricle are depicted in [Figure 2](#). During follow-up, sustained ventricular tachycardia or ventricular fibrillation were documented in 8 patients (9.4%), including 1 patient with SRV (3.2%). Seventeen patients (20.0%) had at least 1 hospitalization for heart failure, including 7 patients with SRV (22.6%).

Response to CRT

[Figure 3](#) summarizes the number of patients assessed at each time point (baseline, 6 months, 12 months, and 24 months).

In the whole cohort, the QRS duration decreased from 168 ± 37.6 to 134 ± 26.5 ms after CRT implantation ($P < .001$). The proportion of CRT responders at 6, 12, and 24 months were 73.2%, 70.6%, and 72.7%, respectively. The median (IQR) systemic ejection fraction improved from 35% (27%–40%) at baseline to 45% (35%–50%) at 6 months ($P < .001$), 45% (34%–50%) at 12 months ($P < .001$), and

Table 1 Patient characteristics at CRT implantation

Characteristic	All (N = 85)	Left ventricle (n = 49)	<i>P</i> [*]	Right ventricle (n = 31)	<i>P</i> [†]	Single ventricle (n = 5)
Patient characteristics						
Age (y)	39.8 ± 20.0	38.1 ± 20.7	.220	43.9 ± 19.8	.207	30.7 ± 7.49
Male	55 (64.7)	36 (73.5)	.046	16 (51.6)	1.000	3 (60.0)
Number of cardiac surgeries	2 (1–2)	2 (1–3)	<.001	1 (0–1.5)	.182	3 (1–4)
NYHA class baseline			.165		.326	
I	6 (7.1)	1 (2.04)		4 (12.9)		1 (20.0)
II	36 (42.4)	22 (44.9)		11 (35.5)		3 (60.0)
III	43 (50.6)	26 (53.1)		16 (51.6)		1 (20.0)
Hospitalization for heart failure	22 (25.9)	17 (34.7)	.079	5 (16.1)	1.000	0 (0.0)
Atrial arrhythmia	45 (52.9)	30 (61.2)	.038	11 (35.5)	.138	4 (80.0)
Systemic ejection fraction (%)	35 (30–42)	40 (30–45)	.022	35 (26.5–40)	.007	45 (40–55)
CRT device						
Cardiac device before CRT	59 (69.4)	34 (69.4)	1	22 (71.0)	.631	3 (60.0)
CRT indication			.314		.011	
Low EF and wide QRS complex	14 (16.5)	10 (20.4)		4 (12.9)		0 (0.0)
Low EF and ventricular pacing	57 (67.1)	30 (61.2)		24 (77.4)		3 (60.0)
Normal EF and ventricular pacing	14 (16.5)	9 (18.4)		3 (9.7)		2 (40.0)
CRT-defibrillator	25 (29.4)	15 (30.6)	1	10 (32.3)	.293	0 (0.0)
CRT approach			.172		.243	
Endovascular	39 (45.9)	26 (53.1)		12 (38.7)		1 (20.0)
Epicardial	35 (41.2)	19 (38.8)		12 (38.7)		4 (80.0)
Hybrid	11 (12.9)	4 (8.2)		7 (22.6)		0 (0.0)
QRS duration before CRT (ms)	168 ± 37.6	172 ± 36.3	.528	166 ± 35.4	.398	127 ± 64.3
QRS pattern			.032		.607	
Right BBB	22 (27.2)	17 (37.0)		4 (13.3)		1 (20.0)
Left BBB	6 (7.4)	4 (8.7)		2 (6.7)		0 (0.0)
Nonspecific conduction delay	1 (1.2)	0 (0.0)		1 (3.3)		0 (0.0)
Ventricular pacing	49 (60.5)	25 (54.3)		21 (70.0)		3 (60.0)
Normal	3 (3.7)	0 (0.0)		2 (6.7)		1 (20.0)
QRS duration after CRT (ms)	134 ± 26.5	139 ± 26.3	.061	127 ± 24.5	.526	113 ± 30.6
Pharmacological therapy						
β-Blockers	48 (56.5)	27 (55.1)	.754	19 (61.3)	.630	2 (40.0)
ACE inhibitors or ARB	63 (74.1)	37 (75.5)	1.000	24 (77.4)	.119	2 (40.0)
Diuretics	44 (51.8)	30 (61.2)	.239	14 (45.2)	.134	0 (0.0)
Aldosterone antagonist	30 (35.3)	18 (36.7)	1.000	12 (38.7)	.146	0 (0.0)
Sacubitril	3 (3.5)	1 (2.0)	.556	2 (6.5)	1.000	1 (0.0)

Values are presented as mean ± SD, median (interquartile range), or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BBB = bundle branch block; CRT = cardiac resynchronization therapy; EF = ejection fraction; NYHA = New York Heart Association.

**P* values between patients with systemic right ventricle and those with systemic left ventricle.

†*P* values between patients with systemic right ventricle and those with single ventricle.

45% (35%–50%) at 24 months (*P* < .001). The proportion of patients in NYHA class I or II increased from 42.9% at baseline to 83.9% at 6 months (*P* < .001), 74.5% at 12 months (*P* = .006), and 76.8% at 24 months (*P* = .009).

In patients with SRV, the QRS duration changed from 166 ± 35.4 to 127 ± 24.5 ms, with a mean decrease of −46 ± 26 ms (vs −35 ± 32 ms in patients with systemic left ventricle; *P* = .16). The decrease in QRS duration was similar in patients with SRV and D-TGA and atrial switch than patients with cc-TGA (−47 ± 22 ms vs −45 ± 29 ms; *P* = .86). The proportion of CRT responders and changes in systemic ejection fraction and NYHA class at the different time points in patients with SRV and in patients with systemic left ventricle are reported in Figure 4. The proportion of CRT responders at 6, 12, and 24 months were 82.6%, 80.0%, and 77.8% in patients with SRV vs 66.7%, 64.3%, and 69.6% in patients with sys-

temic left ventricle (*P* = NS). The proportion of CRT responders at different time points were also comparable between patients with SRV and D-TGA and atrial switch and those with cc-TGA (*P* = NS). The median (IQR) systemic ejection fraction improved from 30% (25%–38%) to 40% (31%–45%) at 6 months (*P* < .001), 40% (30%–45%) at 12 months (*P* = .008), and 40% (30%–40%) at 24 months (*P* = .007) in patients with SRV, and the proportion of patients in NYHA class I or II increased from 34.7% to 91.3% at 6 months (*P* < .001), 80.0% at 12 months (*P* = .04), and 82.3% at 24 months (*P* = .04).

In the whole cohort, CRT implantation for low systemic ejection fraction associated with need for ventricular pacing compared with CRT implantation for low systemic ejection fraction associated with wide QRS complex (odds ratio [OR] 7.2; 95% confidence interval [CI] 1.5–36.4; *P* = .01)

Table 2 Characteristics of patients with SRV

Characteristic	All (N = 31)	cc-TGA (n = 21)	D-TGA with atrial switch (n = 10)	P
Patient characteristics				
Age (y)	43.9 ± 19.8	49.1 ± 21.9	33.0 ± 6.3	.004
Male	16 (51.6)	10 (47.6)	6 (60.0)	.704
Number of cardiac surgeries (IQR)	1 (0–1.5)	0 (0–1)	1 (1–2)	.020
NYHA class baseline				
I	4 (12.9)	4 (19.0)	0 (0.0)	.320
II	11 (35.5)	6 (28.6)	5 (50.0)	
III	16 (51.6)	11 (52.4)	5 (50.0)	
Hospitalization for heart failure	5 (16.1)	5 (23.8)	0 (0.0)	.147
Atrial arrhythmia	11 (35.5)	8 (38.1)	3 (30.0)	1.000
Systemic ejection fraction (%)	35 (26.5–40.0)	35 (28–40)	32.5 (26.3–38.8)	.952
CRT device				
Cardiac device before CRT	22 (71.0)	15 (71.4)	7 (70.0)	1.000
CRT indication				
Low EF and wide QRS complex	4 (12.9)	2 (9.5)	2 (20.0)	.756
Low EF and ventricular pacing	18 (58.1)	13 (61.9)	5 (50.0)	
Normal EF and ventricular pacing	9 (29.0)	6 (28.6)	3 (30.0)	
CRT-defibrillator	10 (32.3)	7 (33.3)	3 (30.0)	1.000
CRT approach				
Endovascular	12 (38.7)	12 (57.1)	0 (0.0)	<.001
Epicardial	12 (38.7)	9 (42.9)	3 (30.0)	
Hybrid	7 (22.6)	0 (0.0)	7 (70.0)	
QRS duration before CRT (ms)	166 ± 35.4	164 ± 32.7	169 ± 41.2	.745
QRS pattern				
Right BBB	4 (13.3)	2 (10.0)	2 (20.0)	.830
Left BBB	2 (6.7)	2 (10.0)	0 (0.0)	
Nonspecific conduction delay	1 (3.3)	1 (5.0)	0 (0.0)	
Ventricular pacing	21 (70.0)	14 (70.0)	7 (70.0)	
Normal	2 (6.7)	1 (5.0)	1 (10.0)	
QRS duration after CRT (ms)	127 ± 24.5	124 ± 20.7	132 ± 30.8	.467
Pharmacological therapy				
β-Blockers	19 (61.3)	12 (57.1)	7 (70.0)	.697
ACE inhibitors or ARB	24 (77.4)	15 (71.4)	9 (90.0)	.379
Diuretics	14 (45.2)	11 (52.4)	3 (30.0)	.280
Aldosterone antagonist	12 (38.7)	9 (42.9)	3 (30.0)	.697
Sacubitril	2 (6.5)	2 (9.5)	0 (0.00)	1.000

Values are presented as mean ± SD, median (interquartile range), or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BBB = bundle branch block; cc-TGA = congenitally corrected transposition of the great arteries; CRT = cardiac resynchronization therapy; D-TGA = D-transposition of the great arteries; EF = ejection fraction; NYHA = New York Heart Association; SRV = systemic right ventricle.

and female sex (OR 11.6; 95% CI 2.0–222.6; $P = .02$) were associated with a higher likelihood of response to CRT. Narrower paced QRS after CRT (131 ± 22 ms vs 161 ± 33 ms; OR 1.7; 95% CI 1.2–2.9 per 10-ms decrement; $P = .01$) were also associated with response to CRT, whereas the observed difference in QRS duration at baseline (170 ± 34 ms vs 186 ± 39 ms; $P = .357$) and in the change of QRS duration (-43 ± 27 vs -32 ± 38 ; $P = .492$) between responders and nonresponders did not reach statistical significance. Specifically among patients with SRV, compared with nonresponders, CRT responders had a higher baseline systemic ejection fraction (40% [40%–45%] vs 30% [25%–36%]; $P = .02$) and a higher proportion of epicardial or hybrid CRT systems (68.4% vs 0.0%; $P = .02$).

Discussion

In this multicenter cohort, one-third of patients with CHD implanted with a CRT device had SRV. CRT in patients with SRV was associated with a high rate (80%) of responders, comparable to that of patients with systemic left ventricle.

Management of heart failure is a major and growing issue in the population with CHD. Despite the lack of evidence, CRT devices have been progressively used, also because alternative options are poor, mainly represented by cardiac transplantation with rare grafts and frequent contraindications in patients with CHD. Most of the studies published on CRT in patients with CHD included patients with tetralogy of Fallot, SRV, or single ventricle. The first results originated from small series where hemodynamic invasive

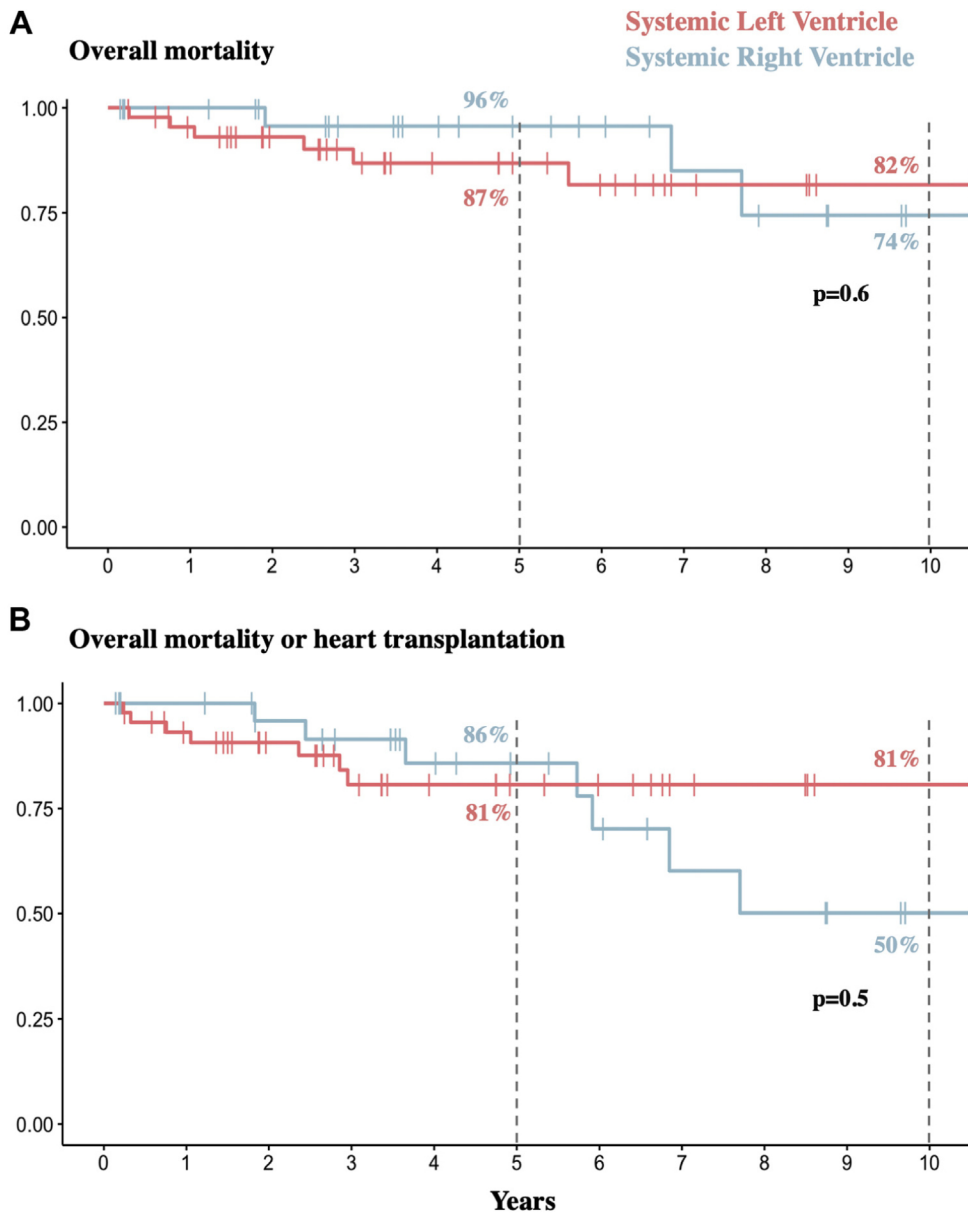


Figure 2 Kaplan-Meier curves of survival free from (A) overall mortality and (B) overall mortality or heart transplantation.

parameters were improved and QRS narrowed by multisite pacing.⁵⁻⁹ Different studies then reported improved ventricular function and patient-reported functional subjective parameters (mainly NYHA classification).¹⁰⁻¹³ However, despite these preliminary data suggesting a positive impact of CRT, firm conclusions cannot be drawn because of the limited number of patients and also because most studies combined patients with heterogeneous types of CHD with results difficult to translate into clinical practice.

The RV clearly differs in embryological origin, anatomy, functional properties, and electrophysiological characteristics as compared with the LV. The crescent-shaped RV is wrapped around the LV, has a unique longitudinal activation pattern, lower oxygen requirement, and lower coronary blood flow.²² In contrast to systemic left ventricle failure, less is known regarding the pathophysiology and outcomes of

different therapeutic options in SRV failure. Studies evaluating CRT specifically in patients with SRV are rare. A first proof-of-concept study included 8 patients over a median follow-up of 17.4 months and demonstrated a significant decrease in QRS duration and an improvement in systemic right ventricular function assessed by radionuclide ventriculography.⁵ Several small series have then demonstrated conflicting results on the efficacy of CRT in patients with SRV. The largest study to date assessing specifically CRT in patients with SRV included 20 patients with cc-TGA and defined *respond to CRT* as an improvement in NYHA class by at least 1 grade or an increase in RV fractional area change of $\geq 10\%$ within 3 months of CRT.¹⁶ Among patients with congestive heart failure, acute improvement was observed in 67% of patients but 25% showed loss of response over a median follow-up period of 4.6 years. When considering

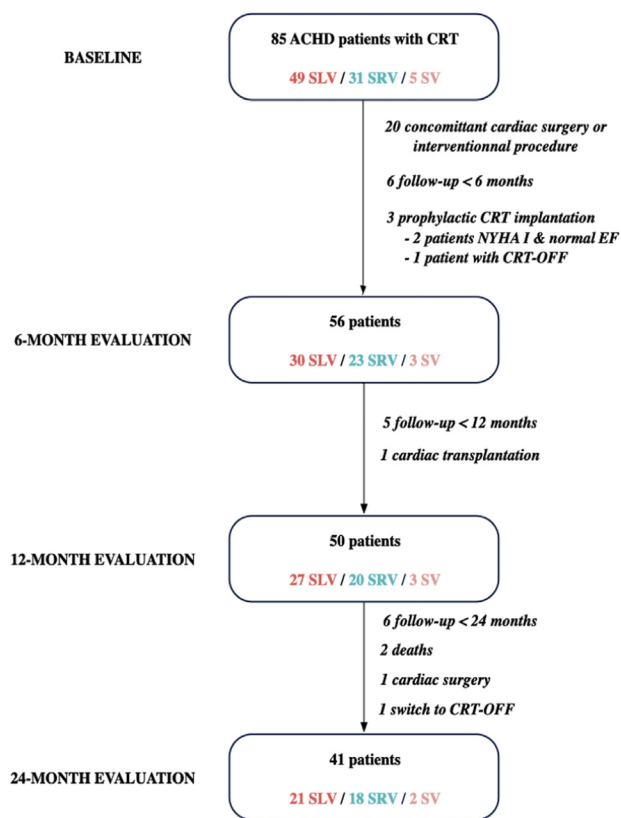


Figure 3 Flowchart of the study. ACHD = adult congenital heart disease; CRT = cardiac resynchronization therapy; EF = ejection fraction; SLV = systemic left ventricle; SRV = systemic right ventricle; SV = single ventricle.

studies including heterogeneous forms of CHD, the largest one included 36 patients with SRV, and among 27 patients with analyzable outcomes, only 13.6% of patients were considered as nonresponders to CRT.²³ Because of the unique features of patients with SRV and also because they represent one of the largest groups of patients with CHD implanted with a CRT device, accumulating specific data in this population is of particular importance and was identified as a major evidence gap and as a high-impact research question by the American Heart Association/American College of Cardiology guidelines committee.¹⁹ Our findings demonstrated a high rate of CRT responders among patients with SRV, with ~80% of patients who had an improvement in functional outcomes or an increase in systemic ejection fraction. It is also interesting to note that the proportion of responders was similar to the whole population, while previous studies had suggested a lesser improvement in patients with SRV than in patients with systemic left ventricle.^{23,24}

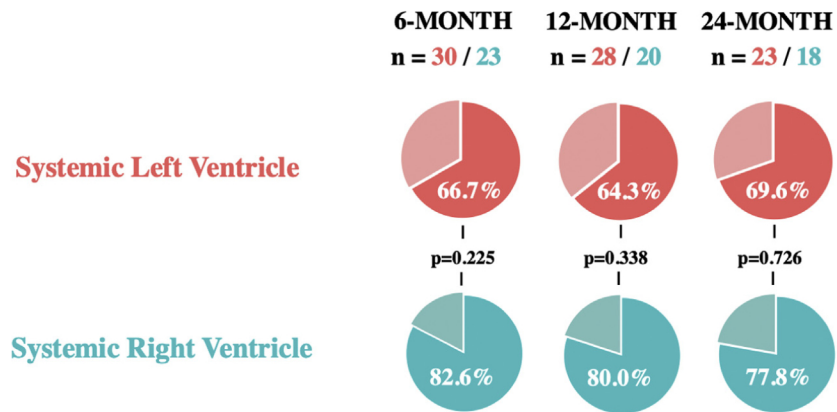
Currently, CRT devices are mainly recommended in international guidelines as a class IIa indication in patients with SRV and (1) systemic ejection fraction $\leq 35\%$ and QRS duration ≥ 150 ms (spontaneous or paced) or (2) preserved systemic ejection fraction undergoing new device placement or replacement with anticipated requirement for significant

(>40%) ventricular pacing.^{21,25} In 2020 European Society of Cardiology guidelines for the management of adult CHDs, biventricular pacing is recommended for patients with cc-TGA in case of complete atrioventricular block or >40% ventricular pacing requirement regardless of systemic ejection fraction, considering data that suggested that it may lead to a better preservation of RV systolic function than LV pacing alone.^{14,26} Considering the limited evidence, the individual risk-benefit ratio remains essential to assess. Our results however demonstrated an acceptable rate of complications, at least when performed in tertiary centers, particularly considering the significant proportion of patients with concomitant cardiac surgery and the frequent need for epicardial or hybrid CRT devices in those patients. Only 1 patient with SRV had acute CRT-related complication (pocket hematoma) and regarding the burden of late complications, 6% of patients had lead dysfunctions and 10% had CRT-related infections during follow-up.

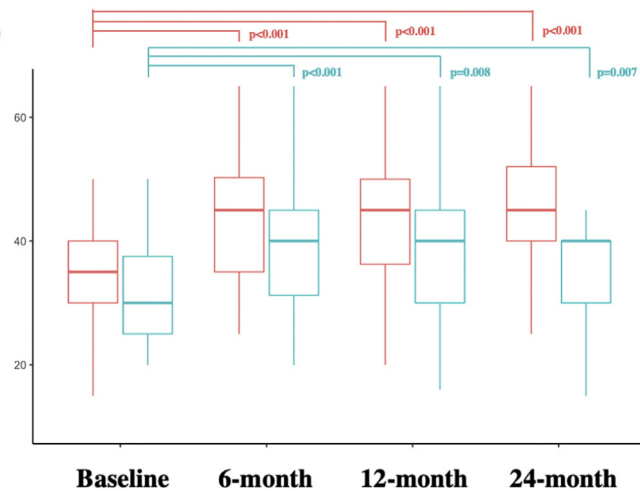
The identification of reliable predictors of CRT response may also help improve patient selection. In our study, CRT implantation with need for ventricular pacing (vs for wide QRS complex), female sex, and narrower paced QRS were associated with a higher likelihood of response CRT in the whole cohort. In patients with SRV, a previous study including patients with cc-TGA suggested that lead location at the RV free wall was associated with better outcomes compared with lead location in the RV outflow tract.¹⁶ We observed in this cohort that the proportion of responders was greater in patients with SRV and a higher baseline systemic ejection fraction and in those with epicardial or hybrid CRT devices. CRT might be less effective in patients with severely advanced systolic dysfunction of the SRV and may help, as previously suggested, to prevent progressive SRV failure.⁵ Epicardial or hybrid approaches might also be associated with easier optimization of lead positioning as compared with endovascular approaches, in particular considering possible coronary venous anatomy abnormalities reported in patients with cc-TGA.²⁷

Less than one-third of patients had CRT-defibrillators, and the majority was implanted in a primary prevention setting (9 primary prevention in 10 patients with SRV and CRT-defibrillator). The experience regarding ICD in patients with SRV is still limited, and considering the paucity of data, ICD implantation in primary prevention is currently a class IIb recommendation.^{21,25} Only 1 patient with SRV had a sustained ventricular arrhythmia documented during follow-up, despite continuous monitoring in all patients offered by CRT devices. Competing risks also have to be considered in those patients, as illustrated by the high burden of nonsudden deaths (mainly related to heart failure) and heart transplantation with incidences of overall mortality or heart transplantation of 14% and 50% at 5 and 10 years, respectively. Moreover, the higher risk of system failure with nontransvenous defibrillators has to be considered in those patients with frequent epicardial or hybrid devices.²⁸

A — Rate of CRT responders (%)



B — Systemic EF (%)



C — NYHA class

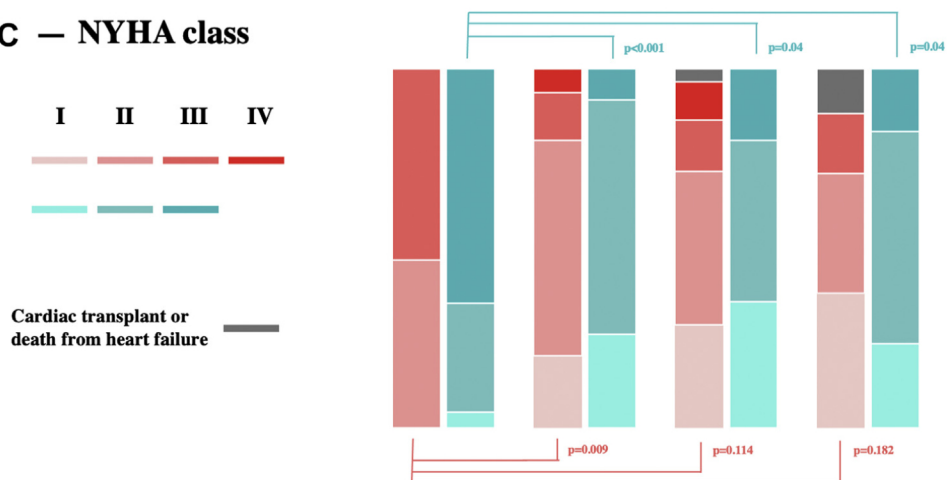


Figure 4 (A) Proportion of cardiac resynchronization therapy (CRT) responders, (B) changes in systemic ejection fraction (EF), and (C) changes in New York Heart Association (NYHA) class. At 12 months, in addition to the 27 patients with systemic left ventricle assessed, the patient with heart transplantation between 6 and 12 months was considered as a nonresponder. At 24 months, in addition to the 20 patients with systemic left ventricle assessed, the same patient and the 2 patients who died of heart failure between 12 and 24 months were considered as nonresponders. Consequently, outcomes at 12 and 24 months are reported in 28 and 23 patients with systemic left ventricle, respectively.

Study limitations

This study was observational and retrospective with inherent biases. The number of patients with SRV included was also

relatively modest. However, this cohort is one of the largest published to date on this specific population, and the focus on this group of patients was important to correlate CRT

with outcomes in a relatively homogeneous population. The assessment of the systemic right ventricular ejection fraction by echocardiography may also be complex, but CRT devices precluded performing repetitive cardiac magnetic resonance imaging to better appreciate changes in SRV function and remodeling. Echocardiograms were interpreted locally, and measurements were not centrally performed in a core laboratory. Last, CRT devices indications and programming were nonuniform and left at the discretion of the local medical team. The exact locations of RV and LV leads were not available in a significant number of cases, particularly in epicardial/hybrid devices; therefore, we were not able to correlate lead position with outcomes. The modest number of patients also precluded to perform multivariate analyses when analyzing factors associated with response to CRT and requires further evaluation.

Conclusion

In this multicenter cohort, ~80% of patients with SRV had functional outcomes or systemic ejection fraction improved by CRT. The proportion of CRT responders was similar in patients with SRV and in patients with systemic left ventricle. These findings need future prospective larger studies to further assess the impact of CRT on harder end points and to identify and validate selection criteria of patients with SRV who are most likely to benefit.

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