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DEVICES

Long-term outcomes of cardiac resynchronization therapy in adult congenital heart disease

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Abstract

Background and Aims: Randomized, controlled trials of cardiac resynchronization therapy (CRT) excluded patients with adult congenital heart disease (ACHD). We sought to explore long-term clinical outcomes.

Methods and Results: In this single-center, observational study, events were collected from hospital records on patients with structural ACHD (sACHD) and adults with ischemic (ICM) or non-ischemic (NICM) cardiomyopathy undergoing CRT. Patients with sACHD (n = 23, age: 41.6 ± 13.5 years [mean ± standard deviation]) and adults with ICM (n = 533) or NICM (n = 458) were followed-up for 4.1 years (median; interquartile range: 2.2-6.1). Total mortality was 5/23 (21.7%; 4.4 per 100 person-years) in sACHD, 221/533 (41.5%; 11.8 per 100 person-years) in ICM, and 154/458 (33.6%; 9.7 per 100 person-years) in NICM. In univariate analyses, total mortality in sACHD was lower than in ICM (hazard ratio [HR]: 0.38; 95% confidence interval [CI] 0.15-0.91), but similar to NICM (HR: 0.48, 95% CI 0.20-1.16). Cardiac mortality in sACHD was similar to ICM (HR: 0.78, 95% CI 0.32-1.92) and NICM (HR: 1.12, 95% CI 0.45-2.78). Heart failure (HF) hospitalization rates were similar to ICM (HR: 0.44, 95% CI 0.11-1.77) and NICM (HR: 0.75, 95% CI 0.18-3.08). In multivariate analyses, no differences emerged in total mortality, cardiac mortality, or HF hospitalization between sACHD and NICM or ICM, after adjustment for age, sex, New York Heart Association class, diabetes, atrial rhythm, QRS duration, QRS morphology, systemic ventricular ejection fraction, and medical therapy.

Conclusion: Total mortality, cardiac mortality, and HF hospitalization after CRT in patients with sACHD was similar to adults with ICM or NICM.

KEYWORDS
adult congenital heart disease, cardiac resynchronization therapy, heart failure, mortality

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for adult patients with heart failure (HF), impaired left ventricular (LV) function, and a wide QRS complex.[1] Supporting evidence has emerged from numerous randomized, controlled trials and meta-analyses thereof.[2] Consequently, CRT is now widely accepted as a Class I indication (level of evidence A) for selected patients with nonischemic (NICM) or ischemic (ICM) cardiomyopathy.

It has been shown that CRT in adult congenital heart disease (ACHD) is feasible[3,4]; the Pediatric and Congenital Electrophysiology Society/Heart Rhythm Society (PACES/HRS) expert consensus statement on the recognition and management of arrhythmias in ACHD[5] states that CRT is indicated in patients with ACHD with sinus rhythm, a systemic ventricular ejection fraction (SVEF) <35%, left bundle branch block (LBBB), a QRS complex >150 ms (spontaneous or paced), and a New York Heart Association (NYHA) class II to IV (ambulatory) symptoms. These indications, which are classified as a level

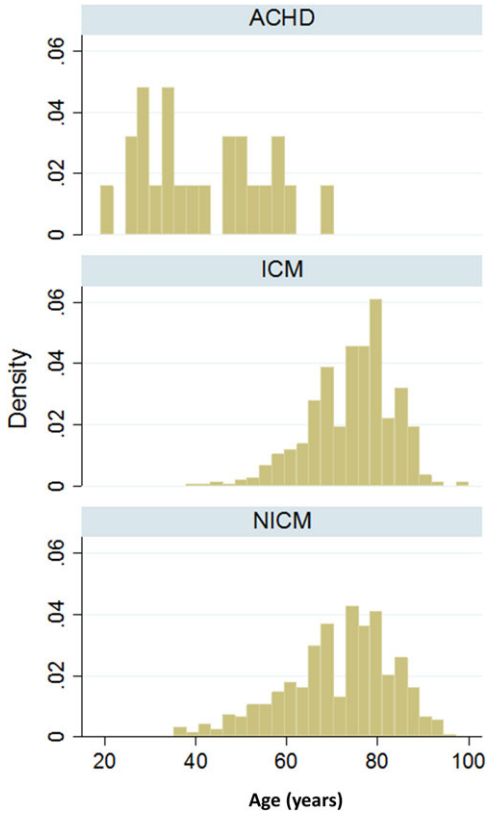

FIGURE 1 Age distribution according to etiology of cardiomyopathy. ACHD = adult congenital heart disease; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy [Color figure can be viewed at wileyonlinelibrary.com]

of evidence "B," are based on presumed surrogate markers of clinical outcomes from adult populations with congenitally normal hearts, none of which have been validated against "hard endpoints" in ACHD. Moreover, no studies of CRT in the pediatric or ACHD population have involved randomization, and clinical outcome data are also lacking, even from observational studies.[5] In addition, not all observational studies of CRT in ACHD have distinguished between structural ACHD (sACHD) and nonstructural ACHD, such as dilated cardiomyopathy and congenital complete heart block.[5] In the absence of firm evidence in its favor, CRT in ACHD is not permitted in some countries, notably Japan.[6]

In the context of the challenges in undertaking randomized, controlled studies in a young, heterogenous population with rare conditions, we sought to compare outcomes of CRT in adults with sACHD, NICM, or ICM.

2 | METHODS

This is a retrospective study of patients with sACHD who had their first CRT device implantation at a tertiary referral center for ACHD (Queen Elizabeth Hospital, Birmingham, United Kingdom) from March 2002 to January 2017. Outcomes were compared with a population of adult patients with NICM or ICM who also underwent CRT device implantation in the same time period. Some adult patients with NICM or ICM have been included in previous publications.[7] The study was approved by the Clinical Audit Department at the Queen Elizabeth Hospital, which permits publication of clinical data for the purposes of service evaluation. The study conforms with the Declaration of Helsinki.

TheUnited Kingdom National Institute of Clinical Excellence (NICE) guidelines in 2007 recommended CRT-pacing (CRT-P) rather than CRT-defibrillation (CRT-D) for patients with NICM and indications for CRT. With a subsequent guideline change in 2014 recommending CRT-D in NICM,[8] the proportion of CRT-D recipients increased thereafter. No specific guidelines have been issued by NICE or indeed any other guideline group as to the choice of CRT-P or CRT-D in the ACHD population. Consequently, device choice was dependent on physician's discretion.

2.1 | Endpoints

The primary endpoint was total mortality and the secondary endpoint was cardiac mortality, which included cardiac transplantation or implantation of a ventricular assist device. We also included the ancillary endpoint of unplanned HF hospitalization. Mortality data were collected through medical records and cross-checked with a national mortality database. Clinical outcome data were collected every 6 months by investigators who were blinded to clinical and imaging data.

2.2 | Device therapy

Device implantation was undertaken using standard transvenous techniques under general or local anesthesia and intravenous sedation, or via a thoracotomy with epicardial lead deployment under general anesthesia. The transvenous implantation technique in patients with sACHD varied according to the anatomy of the systemic ventricle and the location and accessibility of the coronary sinus and its tributaries. Implanters aimed at implanting the LV lead in a posterolateral vein. There was no systematic use of QLV interval, as evidence for this approach predated most of the implantations. The choice of CRT-D and CRT-P was based on the occurrence of sustained ventricular arrhythmias prior to implantation. After implantation, patients were followed-up in dedicated device clinics. Up to 2013, patients in sinus rhythm underwent trans-mitral Doppler-directed optimization of atrioventricular delay using an iterative technique prior to discharge and at every scheduled visit. Routine echocardiographic optimization was abandoned thereafter and was only undertaken in symptomatic nonresponders. Backup atrial pacing was set at 60 beats/min, and the pacing mode was set to DDDR with an interventricular delay of 0-20 ms (left ventricular [LV] first), according to clinician's discretion. In patients with permanent atrial fibrillation, systemic ventricular and nonsystemic ventricular leads were implanted and a CRT generator was used, plugging the atrial port and programming to a ventricular triggered mode, according to physician's choice. Atrioventricular junction ablation was undertaken according to physicians' decision.

TABLE 1 Characteristics of the study group

	sACHD	ICM	NICM	*P*-value
N	23	533	458	
Sex (male), n (%)	13 (56.52)	425 (79.74)	294 (64.19)	<.001
Age (years)	41.6 ± 13.5	74.4 ± 9.2	71.4 ± 11.9	<.001
NYHA class, n (%)				
I	3 (13.64)	20 (3.88)	26 (5.96)	.304
II	3 (13.64)	68 (13.18)	68 (15.6)	
III	15 (68.18)	395 (76.55)	317 (72.71)	
IV	1 (4.55)	33 (6.4)	25 (5.73)	
Device type, n (%)				
CRT-D	6 (26.09)	346 (64.92)	114 (24.89)	<.001
CRT-P	17 (73.91)	187 (35.08)	344 (75.11)	
Upgrades from pacemaker	13 (56.5)	75 (14.07)	98 (21.40)	<.001
Comorbidity, n (%)				
Diabetes mellitus	2 (8.70)	162 (30.39)	88 (19.21)	<.001
Hypertension	1 (4.35)	160 (30.02)	136 (29.69)	.029
CABG	–	148 (27.77)	32 (6.99)	<.001
ECG variables				
Sinus rhythm, n (%)	18 (78.26)	349 (65.48)	286 (62.45)	.228
Atrial fibrillation, n (%)	5 (21.74)	184 (34.52)	172 (37.55)	
LBBB, n (%)	15 (65.22)	426 (79.92)	412 (89.96)	<.001
QRS duration (ms)	170.5 ± 30.8	152.8 ± 21.8	158.2 ± 21.8	<.001
Medication, n (%)				
Loop diuretics	22 (95.65)	513 (96.25)	431 (94.1)	.284
ACEIs/ARAs	21 (91.30)	459 (86.12)	391 (85.37)	.711
β-Blockers	21 (91.30)	395 (74.11)	302 (65.94)	.002
MRAs	11 (47.83)	247 (46.34)	181 (39.52)	.088
SVEF (%)	32.8 ± 12.6	24.2 ± 9.3	25.1 ± 9.5	<.001

Note. Variables are expressed as mean ± standard deviation, unless indicated otherwise.
Abbreviations: ACEIs = angiotensin-converting enzyme inhibitors; ARAs = angiotensin receptor antagonists; CABG = coronary artery bypass grafting; CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; ECG = electrocardiogram; ICM = ischemic cardiomyopathy; LBBB = left bundle branch block; MRAs = mineralocorticoid receptor antagonists; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; sACHD = structural adult congenital heart disease; SVEF = systemic ventricular ejection function.
[a]Differences between the groups from analysis of variance for continuous variables and from chi-squared tests for categorical variables.
[b]Permanent, persistent, and paroxysmal atrial fibrillation (AF).

Patients underwent a clinical assessment on the day prior to implantation and at 1, 3, and every 6 months following device implantation.

2.2.1 | Statistical analysis

Continuous variables are expressed as mean (±standard deviation) and compared using the Student's *t*-test. Categorical variables were compared using the chi-squared statistic. Kaplan-Meier curves and the log-rank test were used to assess survival. Cox proportional hazard models were used to compare risks of the various endpoints. Proportionality hypotheses were verified by visual examination of log (survival) graphs to ensure parallel slopes, and by plotting Schoenfeld residuals. Statistical analyses were undertaken using Stata 14 (StataCorp, College Station, TX, USA). A two-sided $P \leq .05$ was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

The age distribution in the three study groups is shown in Figure 1. As shown in Table 1, patients with sACHD were mostly female ($P < .001$). As expected, they were younger ($P < .001$) and were less likely to have diabetes, hypertension, or a previous coronary artery bypass grafting. No differences emerged with respect to atrial rhythm, but left bundle branch block (LBBB) was less prevalent in the sACHD group ($P < .001$). The sACHD group had a higher proportion of patients on β-blockers ($P = .002$) but the groups were well matched for uptake of loop diuretics, angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor antagonists (ARAs), and mineralocorticoid receptor antagonists. In the sACHD group, the SVEF was higher ($P < .001$) and a

TABLE 2 Characteristics of individual adult congenital heart disease patients

Patient number	Age (years)	Sex	Etiology	Type of ventricle	Operations	Comorbidities	Implantation approach	Device type	Implantation type
1	34	Male	Double outlet RV	Single Ventricle	Fontan procedure	Myocardial infarction, LV thrombus	Transvenous	CRT-P	De novo
2	27	Female	Left atrial isomerism and AVSD	Systemic LV	AVSD repair, left AV valve repair	None	Transvenous	CRT-P	Upgrade
3	55	Male	CCTGA	Systemic RV	TV replacement and MV replacement	Diabetes mellitus, hypertension	Transvenous	CRT-P	De novo
4	29	Male	CCTGA	Systemic RV	Blalock-Taussig shunt, VSD closure and RV-PA conduit, redo RV-PA conduit	Endocarditis	Transvenous	CRT-P	Upgrade
5	47	Female	CCTGA with VSD and pulmonary stenosis	Systemic RV	None	None	Transvenous	CRT-P	Upgrade
6	33	Female	VSD	Systemic LV	PA band, take-down of PA band and VSD closure	Hepatorenal syndrome	Transvenous	CRT-P	De novo
7	49	Male	VSD	Systemic LV	VSD repair	Anomalous coronary arteries	Transvenous	CRT-P	Upgrade
8	32	Male	CCTGA and VSD	Systemic RV	LV-PA conduit, VSD closure	None	Transvenous	CRT-P	Upgrade
9	57	Female	ASD	Systemic LV	ASD closure	Rheumatoid arthritis, hypertension	Transvenous	CRT-D	De novo
10	28	Male	TGA with VSD and pulmonary stenosis	Systemic RV	Waterston shunt, Rastelli procedure, RV-PA conduit	Hepatorenal syndrome	Transvenous	CRT-D	De novo
11	19	Female	CCTGA	Systemic RV	PA band and take-down of PA band	None	Transvenous	CRT-P	Upgrade
12	36	Male	Pulmonary atresia and VSD	Systemic LV	Blalock-Taussig shunt, RV-PA conduit, AVR, aortic root and arch, redo RV-PA conduit	None	Transvenous	CRT-P	De novo

(Continues)

TABLE 2 (Continued)

Patient number	Age (years)	Sex	Etiology	Type of ventricle	Operations	Comorbidities	Implantation approach	Device type	Implantation type
13	50	Male	TOF	Systemic LV	TOF repair, PV replacement	None	Transvenous	CRT-D	Upgrade
14	26	Female	CCTGA	Systemic RV	None	None		CRT-P	Upgrade
15	48	Female	ASD	Systemic LV	ASD closure, MV repair	None	Transvenous	CRT-P	Upgrade
16	43	Female	Ebstein anomaly and ASD	Systemic LV	ASD closure, TV replacement	None	Surgical epicardial	CRT-P	De novo
17	33	Female	CCTGA	Systemic RV	Blalock-Taussig shunt, VSD closure, pulmonary valvotomy, MV repair, PV replacement	None	Surgical epicardial	CRT-P	Upgrade
18	54	Female	VSD	Systemic LV	VSD repair	None	Transvenous	CRT-D	De novo
19	28	Male	Double outlet RV	Single Ventricle	Cavopulmonary shunt, Fontan procedure	None	Surgical epicardial	CRT-P	Upgrade
20	59	Male	TOF	Systemic LV	Blalock-Taussig shunt, TOF repair, PV replacement	Membranous nephropathy	Transvenous	CRT-P	Upgrade
21	40	Male	AVSD	Systemic LV	Left AVSD repair, left AV valve replacement	None	Transvenous	CRT-P	Upgrade
22	60	Male	TOF	Systemic LV	TOF repair, PV replacement	None	Transvenous	CRT-D	De novo
23	69	Male	CCTGA	Systemic RV	None	Myocardial infarction	Transvenous	CRT-D	De novo

Abbreviations: ASD = atrial septal defect; AV = atrioventricular; AVSD = atrioventricular septal defect; CCTGA = congenitally corrected transposition of the great arteries; CRT-D = cardiac resynchronization therapy-defibrillation; CRT-P = cardiac resynchronization therapy-pacing; LV = left ventricle; MV, mitral valve; PA = pulmonary artery; PV = pulmonary valve; TGA = transposition of the great arteries; TOF = tetralogy of Fallot; RV = right ventricle; TV = tricuspid valve; VSD = ventricular septal defect.

TABLE 3 Univariate analyses

	Events		
	ACHD (n = 23)	ICM (n = 533)	NICM (n = 458)
Total mortality	5 (21.7)	221 (41.5)	154 (33.6)
Cardiac mortality	5 (21.7)	106 (19.9)	67 (14.6)
HF hospitalization	2 (8.69)	84 (15.8)	45 (9.82)

Note. Results are expressed in terms of absolute number and percentage of events. ACHD = adult congenital heart disease; HF = heart failure; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy.

greater proportion of patients underwent upgrades from pacemaker to CRT ($P < .001$). The characteristics of individual patients and operation details are shown in Table 2.

3.2 | Outcomes

Over 4.1 years (median 4.1 years; interquartile range: 2.2-6.1 years), total mortality was 5/23 (21.7%; 4.4 per 100 person-years) in the sACHD group, 221/533 (41.5%; 11.8 per 100 person-years) in the ICM group, and 154/458 (33.6%; 9.7 per 100 person-years) in the NICM group (Table 3). There were two patients who underwent implantations of a LV assist device, one in the ICM group and one in the NICM group. None underwent cardiac transplantation. Kaplan-Meier survival analyses are shown in Figure 2. In univariate Cox proportional hazards models, total mortality in sACHD was lower than in ICM (hazard ratio [HR]: 0.38; 95% confidence interval [CI] 0.15-0.91), but similar to NICM (HR: 0.48, 95% CI 0.20-1.16). Cardiac mortality in sACHD was similar to ICM (HR: 0.78, 95% CI 0.32-1.92) and NICM (HR: 1.12, 95% CI 0.45-2.78). Similarly, HF hospitalization was similar to ICM (HR: 0.44, 95% CI 0.11-1.77) and NICM (HR: 0.75, 95% CI 0.18-3.08). Age, sex, NYHA class, diabetes, atrial rhythm, QRS duration, LVEF, and treatment with loop diuretics, ACEIs/ARAs, and β-blockers also emerged as significant predictors of total mortality (Online Appendix) and these variables were included in multivariate analyses. Multivariate analyses showed no differences in total mortality, cardiac mortality, or HF hospitalization between sACHD and ICM or NICM (Table 4).

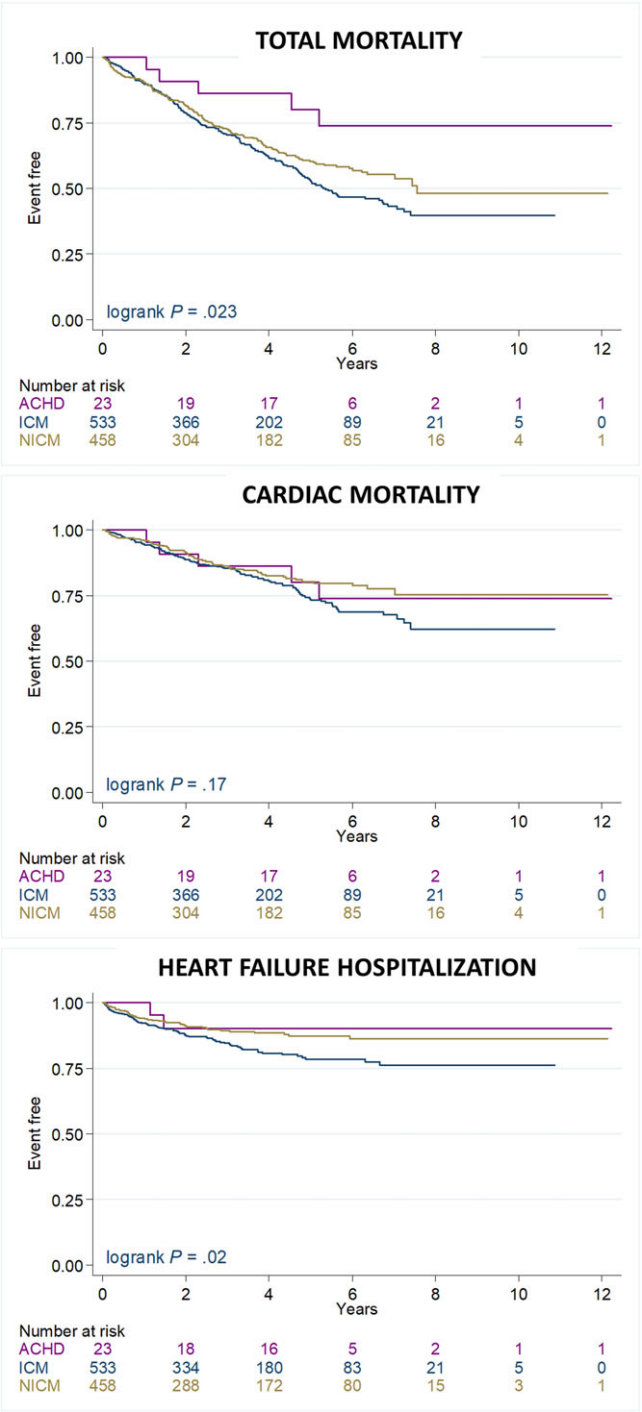

FIGURE 2 Clinical outcomes after cardiac resynchronization therapy according to etiology of cardiomyopathy. ACHD = adult congenital heart disease; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This is the first study to address long-term outcomes of CRT in patients with ACHD.[5] We found that after CRT, total mortality, cardiac mortality, and HF hospitalization in sACHD were similar to adults with ICM or NICM, after adjustment for potential confounders.

Although CRT is being undertaken in the pediatric and adult population with sACHD, studies in its favor have only focused on surrogate predictors of outcome. In a study of 20 patients, Sakaguchi et al showed that in a mixed population of children and adult patients with a systemic LV or single ventricular physiology, CRT led to a reduction in ventricular volume.[9] In a retrospective study comprising children with CHD (n = 73) or cardiomyopathy (n = 16) (median age 12.8 years; follow-up of 4 months), the SVEF improved after CRT.[4] In a retrospective study of 60 children and adults with CHD aged between 5 months and 47 years, which included 46 patients with ACHD and 14 patients with dilated cardiomyopathy (mean age 15 years), CRT was associated with an increase in SVEF from 36% to 42% ($P < .001$) and an improvement in functional status was observed in 87% of patients with follow-up data.[10] Merchant et al also found that in adult patients with repaired tetralogy of Fallot, improvements in LVEF were

TABLE 4 Univariate and multivariate analyses

	sACHD vs ICM				sACHD vs NICM			
Univariate analyses								
Total mortality	0.38	0.15	0.91	0.031	0.48	0.20	1.16	0.103
Cardiac mortality	0.78	0.32	1.92	0.592	1.12	0.45	2.78	0.809
HF hospitalization	0.44	0.11	1.77	0.247	0.75	0.18	3.08	0.685
Multivariate analyses								
Total mortality	1.27	0.42	3.79	0.674	2.66	0.75	9.41	0.128
Cardiac mortality	3.19	0.98	10.4	0.054	2.65	0.66	10.6	0.168
HF hospitalization	1.51	0.29	7.88	0.625	1.95	0.38	10.0	0.422

Notes. Comparison of events in patients with sACHD, using ICM and NICM as reference. Results are expressed in terms of hazard ratios and 95% confidence intervals. In multivariate analyses, there was covarite adjustment for age, sex, New York Heart Association class, diabetes, atrial rhythm, QRS duration, left ventricular ejection fraction, and treatment with loop diuretics, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists, and β-blockers as covariates (see Online Appendix).
Abbreviation: HF = heart failure; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; sACHD = structural adult congenital heart disease.

sustained after 53.4 months.[11] In a recent retrospective study including 48 patients with ACHD (median age: 47 years) followed-up over a median of 2.6 years, 77% responded to CRT either by improvement of NYHA functional class and/or systemic ventricular function.[3] These data, which are based on surrogate outcome measures, are consistent with our findings that outcomes of CRT in sACHD are similar to adult patients with NICM or ICM.

In this study, more than half of patients with sACHD were upgraded from pacemakers to CRT. This is not unexpected, as both sACHD and operations for sACHD lead to conduction system disturbances. Although we do not have access to the SVEF prior to pacemaker implantation, the SVEF at the time of upgrade was severely impaired. This could be due to the natural progression of CHD, but we cannot discount the possibility that subpulmonary ventricular pacing may have contributed to a deterioration in systemic ventricular function. In this respect, right ventricular (RV) pacing is associated with impairment of LV function and a risk of HF in adult patients with NICM or ICM.[12–15] In patients with sick sinus syndrome, up to 40% develop HF with RV pacing.[16,17] In the Dual Chamber and VVI Implantable Defibrillator (DAVID) study[12,18] and the Mode Selection Trial (MOST),[13] RV pacing was also associated with a higher risk of HF hospitalization. In patients with CHD, Moak et al showed an improvement in clinical status after upgrading from pacemakers to CRT in six patients aged 11.3 years with NICM.[19] No data are available in patients with sACHD. Unfortunately, our sample is also too small to explore the effects of upgrading to CRT in sACHD. It would appear, however, that the long-term outcome of CRT in patients with sACHD is comparable to adult patients with NICM, despite the fact that more than half of patients were upgraded from pacemakers. Whether or not pacing the systemic ventricle in patients with sACHD and conventional indications for pacing is preferable to pacing the nonsystemic ventricle remains unexplored.

In this study, patient selection for CRT was driven by the presence of HF symptoms, a wide QRS complex (intrinsic or paced) and impaired SV function, in the background of maximum tolerated medical therapy. Importantly, there will be a selection bias, which was not addressed, insofar as some sACHD patients would not have undergone CRT because of problems with access to peripheral or coronary sinus veins. Physician preference therefore played a role in patient selection.

4.1 | Limitations

The small sample size is the main limitation of this study. Given the trends observed herein, larger numbers could show that CRT is better in ACHD after CRT compared to non-ACHD. Clearly, a congenitally abnormal heart is not the same as a structural normal heart with acquired disease. By definition, age is an inescapable covariate of ACHD. Although we have included age in statistical analyses, the biological interaction between age and ACHD cannot be corrected for by statistical means. Caution is therefore appropriate when interpreting the results of these analyses. Unfortunately, follow-up echocardiograms were not systematically collected and therefore, we are unable to comment on the effects of CRT on LV reverse remodeling. Last, we do not have control groups that were not treated with CRT and therefore, we cannot comment on the relative benefit of CRT, but only on the possible effects of the underlying "substrate."

5 | CONCLUSIONS

We found that after CRT, total mortality, cardiac mortality, or HF hospitalization in sACHD was similar to patients with ICM or NICM. Our findings have emerged in the context that observational studies in the sACHD have not addressed long-term outcomes in patients with sACHD and that a randomized controlled trial of CRT in this patient population is unlikely to emerge.

CONFLICT OF INTERESTS

F.L. is a consultant and has received research support from Medtronic Inc., St. Jude Medical, Boston Scientific, and LivaNova. H.M. is a consultant for Spectranetics. Other authors report no conflict of interest.

Role of the Sponsors

The sponsors had no input in the design and conduct of the study; the collection, management, analysis or interpretation of the data; or in the preparation, review, or approval of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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