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ORIGINAL ARTICLE

Long-Term Outcomes of Cardiac Resynchronization Therapy in Patients With Repaired Tetralogy of Fallot: A Multicenter Study

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BACKGROUND: A growing number of patients with tetralogy of Fallot develop left ventricular systolic dysfunction and heart failure, in addition to right ventricular dysfunction. Although cardiac resynchronization therapy (CRT) is an established treatment option, the effect of CRT in this population is still not well defined. This study aimed to investigate the early and late efficacy, survival, and safety of CRT in patients with tetralogy of Fallot.

METHODS: Data were analyzed from an observational, retrospective, multicenter cohort, initiated jointly by the Pediatric and Congenital Electrophysiology Society and the International Society of Adult Congenital Heart Disease. Twelve centers contributed baseline and longitudinal data, including vital status, left ventricular ejection fraction (LVEF), QRS duration, and NYHA functional class. Outcomes were analyzed at early (3 months), intermediate (1 year), and late follow-up (≥2 years) after CRT implantation.

RESULTS: A total of 44 patients (40.3±19.2 years) with tetralogy of Fallot and CRT were enrolled. Twenty-nine (65.9%) patients had right ventricular pacing before CRT upgrade. The left ventricular ejection fraction improved from 32% [24%–44%] at baseline to 42% [32%–50%] at early follow-up (P<0.001) and remained improved from baseline thereafter (P≤0.002). The QRS duration decreased from 180 [160–205] ms at baseline to 152 [133–182] ms at early follow-up (P<0.001) and remained decreased at intermediate and late follow-up (P≤0.001). Patients with upgraded CRT had consistent improvement in left ventricular ejection fraction and QRS duration at each time point (P≤0.004). Patients had a significantly improved New York Heart Association functional class after CRT implantation at each time point compared with baseline (P≤0.002). The transplant-free survival rates at 3, 5, and 8 years after CRT implantation were 85%, 79%, and 73%.

CONCLUSIONS: In patients with tetralogy of Fallot treated with CRT consistent improvement in QRS duration, left ventricular ejection fraction, New York Heart Association functional class, and reasonable long-term survival were observed. The findings from this multicenter study support the consideration of CRT in this unique population.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: bundle branch block ■ cardiac resynchronization therapy ■ electrophysiology ■ heart failure ■ tetralogy of Fallot

Early surgical repair for tetralogy of Fallot (TOF) has dramatically increased survival into adulthood, and advances in adult care over the last 2 decades have further improved long-term outcomes.[1–3] Although the late clinical course of patients with TOF is often characterized by the progression of right ventricular dysfunction,

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WHAT IS KNOWN?

- A growing number of patients with tetralogy of Fallot develop left ventricular systolic dysfunction, in addition to right ventricular dysfunction.
- There is limited experience and conservative recommendations for cardiac resynchronization therapy in patients with tetralogy of Fallot, which is in part attributable to unfavorable outcomes of cardiac resynchronization therapy in patients with right bundle branch block.

WHAT THE STUDY ADDS

- Long-term cardiac resynchronization therapy in patients with tetralogy of Fallot is characterized by improved QRS duration, left ventricular ejection fraction, and New York Heart Association functional class with reasonable survival and low rate of device-related complications.
- Consistent improvement was observed in patients with prior right ventricular pacing and/ or reduced left ventricular ejection fraction.
- De novo cardiac resynchronization therapy was not associated with persisting shortening of QRS duration and increase in left ventricular ejection fraction during long-term follow-up.

Nonstandard Abbreviations and Acronyms

CHD	congenital heart disease
CRT	cardiac resynchronization therapy
LVEF	left ventricular ejection fraction
NYHA	New York Heart Association
RBBB	right bundle branch block
RVF	right ventricular function
TOF	tetralogy of Fallot

a growing number of patients develop concomitant left ventricular systolic dysfunction.[4,5] Left ventricular systolic dysfunction in patients with TOF has been associated with high rates of life-threatening ventricular arrhythmia, progression of heart failure, and increased mortality.[6–9]

For patients with TOF with end-stage heart failure, no specific therapy has been shown to prevent or delay heart transplantation.[10,11] Guidelines for the treatment of heart failure in patients with congenital heart disease (CHD) propose cardiac resynchronization therapy (CRT) as a potential therapy in patients with electrical-mechanical dyssynchrony.[10–13] However, the level of evidence is currently limited by small and heterogeneous study populations and limited follow-up durations, particularly in patients with TOF.[14–18] The limited experience and conservative recommendations for CRT in patients with TOF are in part attributable to unfavorable outcomes of CRT in patients with right bundle branch block (RBBB), which is present in the majority of the repaired TOF population.[19,20]

However, due to the increasing number of patients with TOF with heart failure, there is a need for more data on the outcomes of CRT in this specific population. Therefore, this international multicenter study aimed to investigate the early and late efficacy, survival, and safety of CRT in patients with TOF.

METHODS

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

Data were analyzed from an observational, retrospective, multicenter cohort, which was initiated by the joint Pediatric and Congenital Electrophysiology Society and the International Society of Adult Congenital Heart Disease electrophysiology research collaborative. Patients were identified from 12 centers in the United States, Canada, and Europe. Institutional review board approval was obtained at each site, and informed consent was waived. The study was conducted according to the principles of the Declaration of Helsinki.

All pediatric and adult patients with TOF undergoing CRT were included. Given the study objective to assess CRT efficacy, patients who received biventricular pacemaker for complete heart block without prior single-site RV pacing, as well as patients who received single-site RV resynchronization were excluded. All retrospective data available until December 2022 were collected and transmitted to the principal investigator at the Erasmus Medical Center using the Research Electronic Data Capture Web application.

Data were retrieved from medical records and included demographic characteristics, associated CHD, date and types of cardiac procedures, comorbidities, pharmacological therapy before CRT implantation, indication and CRT device-related parameters, New York Heart Association (NYHA) classification, electrocardiographic parameters, and echocardiographic parameters.[12] ECGs were reviewed for rhythm and duration of the QRS complex. A significantly wide QRS complex was defined as a (spontaneous or paced) QRS duration of ≥150 ms.[12] Echocardiographic parameters included left ventricular ejection fraction (LVEF) and qualitative right ventricular function (RVF). LVEF ≤35% was regarded as reduced LVEF, and RVF was graded as normal (1), mildly (2), moderately (3), or severely (4) impaired based on echocardiography.[12]

LVEF, RVF, QRS duration, and NYHA functional class were collected before CRT implantation (baseline) and at predefined intervals during follow-up. Outcomes were analyzed at early (3 months), intermediate (1 year), and late follow-up (≥2 years) after CRT implantation. These time points were selected to assess the longitudinal response to CRT at homogeneous intervals. Changes in RVF were not evaluated in patients undergoing concomitant surgical repair at CRT placement. If surgical/transcatheter pulmonary valve replacement occurred during follow-up, changes were limited to time points before these events. Additional outcomes included early and late (>30 days) device-related complications, congestive heart failure hospitalization, heart transplantation and if applicable, cause of death.

Statistical Analysis

Normality was assessed using the Shapiro-Wilk test. Data are reported as mean±SD for normally distributed continuous variables and median with interquartile range for skewed data. Categorical (or dichotomous) data are presented as numbers and percentages. Pairwise deletion statistics, using either the Student *t* test or Wilcoxon signed-rank test, was used to assess changes in LVEF, QRS duration, NYHA functional class, and RVF at different time points during follow-up with those at baseline. Consequently, baseline values differ between various time point analyses due to missing data or loss of follow-up. Student *t* test or Mann-Whitney *U* test was used to compare differences between patient groups. Transplant-free survival after CRT implantation was assessed by Kaplan–Meier Survival analysis. Univariate Cox regression analysis was performed to determine factors associated with readmission, heart transplantation, and mortality. Hazard ratios were reported with 95% CIs. A $P<0.05$ was considered statistically significant. For comparisons that require adjustment for multiple testing, corrected *P* values will be reported using Bonferroni correction. Statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY).

RESULTS

Study Population

A total of 44 patients (29 [65.9%] males) with TOF and CRT were enrolled from 12 participating centers. Patient characteristics are presented in Table 1. Mean age at CRT implantation was 40±19 years. CRT was indicated mainly in patients with reduced LVEF and paced-wide QRS complexes (n=14, 31.8%) or reduced LVEF and need for ventricular pacing (n=12, 27.3%). CRT device was also implanted in 15 (34.1%) patients with normal LVEF and paced-wide QRS complex. Three (6.8%) patients with normal LVEF, RVF dysfunction, and intrinsic-wide QRS complex underwent cardiac surgery and concomitant CRT implantation. During CRT implantation, most patients were in NYHA functional class II (32.6%) or III (54.1%) and only a minority were in NYHA functional class I (14%). RVF was moderately or severely diminished in 55.6% of patients before CRT implantation, 46.7% of whom also had reduced LVEF.

Table 1. Baseline Table

	Overall
Patient characteristics	
Age, y	40.3±19.2
Male (n)	29 (65.9%)
LVEF (%)	30 (21–40)
QRS duration (ms)	182 (160–204)
NYHA functional class	3.0 (2.0–3.0)
I	6 (14.0%)
II	14 (32.6%)
III	22 (51.2%)
IV	1 (2.3%)
Ventricular pacing (n)	29 (65.9%)
CRT indication (n)	
Low EF and wide QRS complex	12 (27.3%)
Low EF and ventricular pacing	14 (31.8%)
Normal EF and ventricular pacing	15 (34.1%)
Normal EF and wide QRS complex	3 (6.8%)
No of surgeries (n)	3 (1–4)
Coronary artery disease (n)	16 (31.8%)
Diabetes (n)	10 (22.7%)
Hypercholesteremia (n)	12 (27.3%)
Hypertension (n)	16 (36.4%)
Severe kidney failure (eGFR ≤30; n)	11 (25%)
Pharmacological therapy (n)	
Diuretics	35 (79.5%)
ACE inhibitors or ARB	35 (79.5%)
Digoxin	15 (34.1%)
AADI	2 (4.5%)
AADII (+ β-blockers)	16 (36.4%)
AADIII	8 (18.2%)
AADIV	1 (2.3%)
AADV	9 (20.5%)

AAD indicates antiarrhythmic drugs; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association

CRT Systems

CRTs were implanted as the initial cardiac implantable device in 15 (34.1%) patients (de novo CRT) and in the setting of chronic RV pacing in the remaining 29 (65.9%) patients (CRT upgrade). All patients with de novo CRT had complete RBBB morphology. CRT device capability included defibrillation (CRT-D) in the majority of patients (n=33, 75.0%) (Table 2). CRT devices were completely epicardial in 13 (29.5%) patients, endovascular in 23 (52.3%), and combined in 8 (18.2%) patients (with an epicardial LV lead in 7). The LV lead was positioned near the basal segment (n=8, 18.2%), mid-segment (n=25, 56.8%) or apex (n=11, 25.0%). Early device-related complications consisted of pocket hematoma in 2 patients. Late device-related complications included lead revision for lead dislodgement (n=2) and emergent pacemaker generator replacement (n=1), due to unexpected battery depletion. Three patients had a nondevice-related cerebrovascular accident late after CRT implantation.

Longitudinal Functional Outcomes

Longitudinal follow-up of LVEF after CRT implantation is shown in Figure 1. During the early follow-up period,

Table 2. CRT Device Characteristics

	Overall (n)
De novo CRT	15 (34.1%)
CRT defibrillator	33 (75.0%)
CRT approach	
Epicardial	13 (29.5%)
Endocardial	23 (52.3%)
Mixed	8 (18.2%)
CRT lead location	
Basal LV	8 (18.2%)
Mid LV	25 (56.8%)
Apical LV	11 (25.0%)
Concomitant cardiac surgery	9 (20.5%)

CRT indicates cardiac resynchronization therapy; and LV, left ventricle.

assessments of LVEF were available for 25 patients (3.0 [1.0–4.0] months after CRT implantation). Further assessments were available for 29 and 33 patients at intermediate (1.0 [0.8–1.1] years) and late follow-up (5.9 [2.0–8.6] years), respectively. LVEF significantly improved after CRT implantation from 32% [24%–44%] at baseline to 42% [32%–50%] at early follow-up (P<0.001) and remained improved during intermediate (35% [20%–41%] versus 40% [31%–53%]; P=0.001), and late follow-up (28% [20%–39%] versus 35% [25%–49%]; P=0.002) compared with baseline. The proportion of patients with at least 10% improvement in LVEF was 40%, 52%, and 30% at early, intermediate, and late follow-up respectively.

ECGs were available for 34, 31, and 36 patients at early, intermediate, and late follow-up (1.7 [0.5–3.0] months, 1.0 [0.9–1.1] years, and 4.3 [2.2–7.6] years, respectively). As shown in Figure 1, QRS duration decreased significantly after CRT implantation from 180 (160–205) ms to 152 (133–182) ms at early follow-up (P<0.001). QRS duration remained shortened at intermediate (184 [164–204] ms versus 158 [140–180] ms; P<0.001) and late follow (180 [160–200] ms versus 159 [141–186] ms; P=0.001) compared with baseline.

NYHA functional class assessment was available in 30 patients at early and intermediate follow-up (2.8 [1.1–3.0] months, 1.0 [0.8–1.1] years, respectively), and in 32 patients at late follow-up (5.1 [2.6–8.4] years). Bar plots in Figure 2 demonstrate the changes in the NYHA functional class after CRT implantation. Patients had a significantly lower NYHA functional class after CRT implantation at each time point compared with baseline (P=0.002, P≤0.001, and P≤0.001, respectively). The proportion of patients in NYHA functional class I or II at early, intermediate and late follow-up was 87%, 90%, and 78%, compared with 45% at baseline.

Qualitative RVF assessment was available in 16 patients at early follow-up (3.1 [3.0–3.7] months) and in 18 patients at late follow-up (2.2 [1.8–6.4] years). Figure 3 demonstrates changes in qualitative RVF at different time points. Compared with baseline measurement, RVF improved significantly at late follow-up (P=0.016), although not yet at early follow-up (P=0.218). More specifically, 38% and 55% of the patients demonstrated

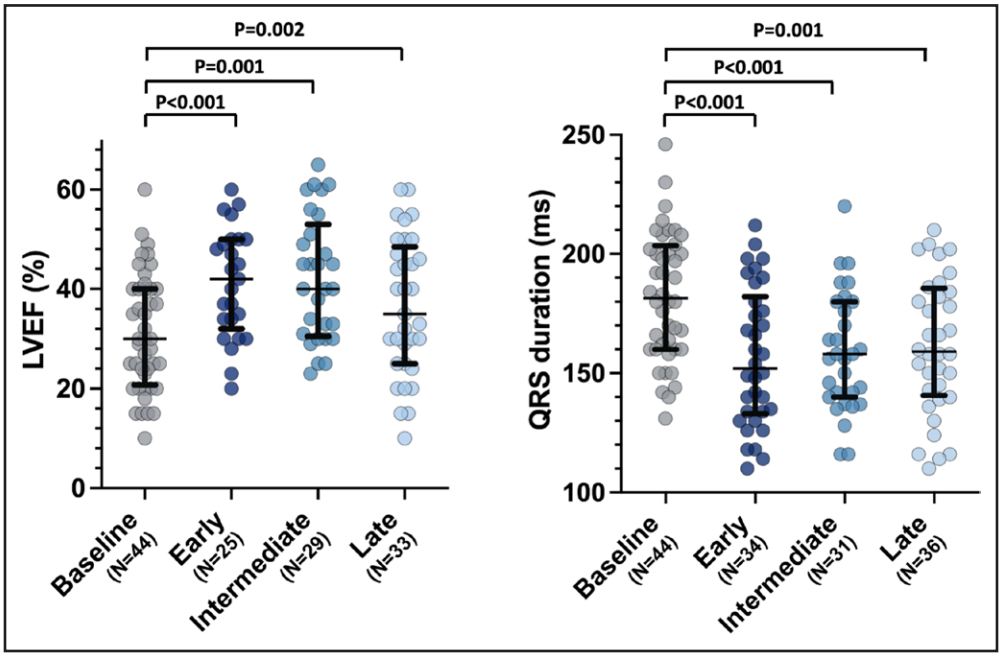

Figure 1. Changes in left ventricular ejection fraction (LVEF) and QRS duration after cardiac resynchronization therapy (CRT) implantation.
Left and right scatter plots demonstrate LVEF and QRS duration after CRT implantation at different time points, compared with baseline. Corrected P values are presented in the figure..

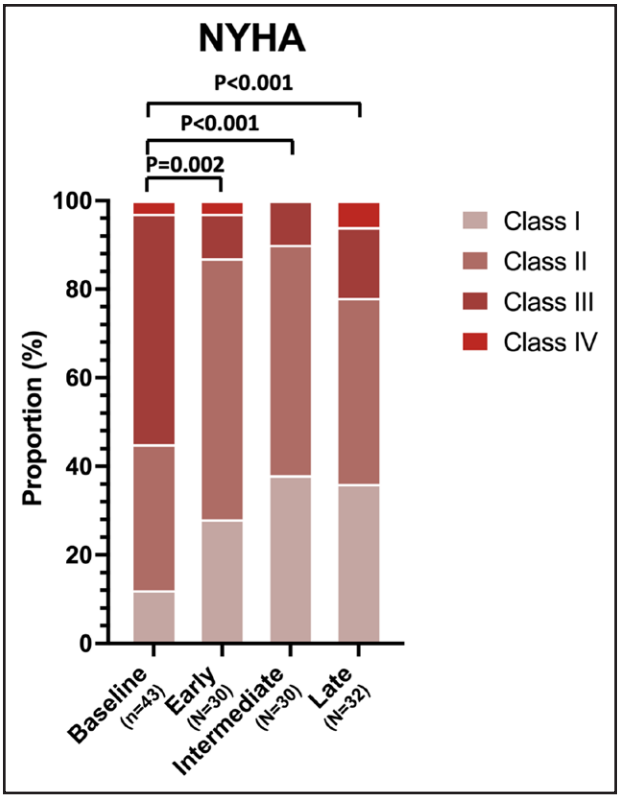

Figure 2. Changes in New York Heart Association (NYHA) functional class after cardiac resynchronization therapy (CRT) implantation.
Bar plots demonstrate NYHA function class after CRT implantation at different time points, compared with baseline. Corrected *P* values are presented in the figure.

improvement in RVF at early and late follow-up, respectively.

Mortality

A total of 8 (18.2%) patients died, and 2 (4.5%) patients underwent heart transplantation. Cardiogenic shock was the main cause of death in 6 patients, and for the remaining 2 patients, the cause of death was unknown. Overall, the median follow-up time was 5.1 (2.0–7.6) years and time from CRT implantation to death was 3.5 (0.8–9.6) years. The transplant-free survival rates at 3, 5, and 8 years after CRT implantation were 85%, 79%, and 73%, respectively. The transplant-free survival rates without heart failure hospitalization were 83%, 73%, and 65%, respectively at 3, 5 and 8 years after CRT implantation. As summarized in Table S1, predictors for mortality, heart transplantation, and heart failure hospitalization could not be identified.

Reduced LVEF versus Preserved LVEF

Twenty-seven (61.3%) patients had at least moderately reduced LVEF (24% [20%–29%]) before CRT implantation, while 17 (38.6%) had a preserved LVEF (41% [40%–47%]). Figure 4 demonstrates the changes after CRT implantation in both groups separately. As shown in the upper panel of Figure 4, CRT in patients with reduced LVEF demonstrated an improved LVEF and shortened QRS duration at each time point (all $P \leq 0.007$). CRT in patients with preserved LVEF also resulted in LVEF improvement at early follow-up (45% [40%–49%] versus 50% [47%–56%]; $P=0.012$). However, at intermediate and late follow-up, LVEF was no longer improved compared with baseline. Similar to patients with reduced LVEF, patients with preserved LVEF also had a decrease in QRS duration at early and intermediate follow-up (202 [159–214] versus 158 [128–192] ms; $P=0.010$; 190 [160–220] versus 156 [137–180] ms; $P=0.014$, respectively). At late follow-up, there was a trend toward a decreased QRS duration compared with baseline in patients with preserved LVEF (179 [155–227] versus 159 [140–176] ms; $P=0.075$). Table S2 describes the effect of CRT in both groups in detail.

De novo CRT versus Previous Ventricular Pacing

Twenty-nine (65.9%) patients had RV pacing before CRT implantation. De novo CRT patients did not differ in baseline LVEF, QRS duration, or NYHA functional class compared with patients with prior RV pacing who received an upgrade (all $P>0.05$). Figure 5 demonstrates the effect of CRT in both groups separately. In patients with previous RV pacing, LVEF, and QRS duration improved at early, intermediate,

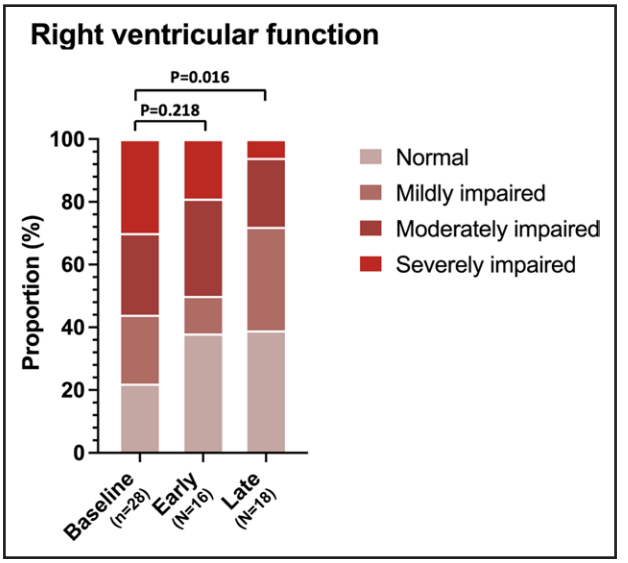

Figure 3. Changes in right ventricular function after cardiac resynchronization therapy (CRT) implantation.
Bar plots demonstrate right ventricular function after CRT implantation at different time points, compared with baseline. Corrected *P* values are presented in the figure.

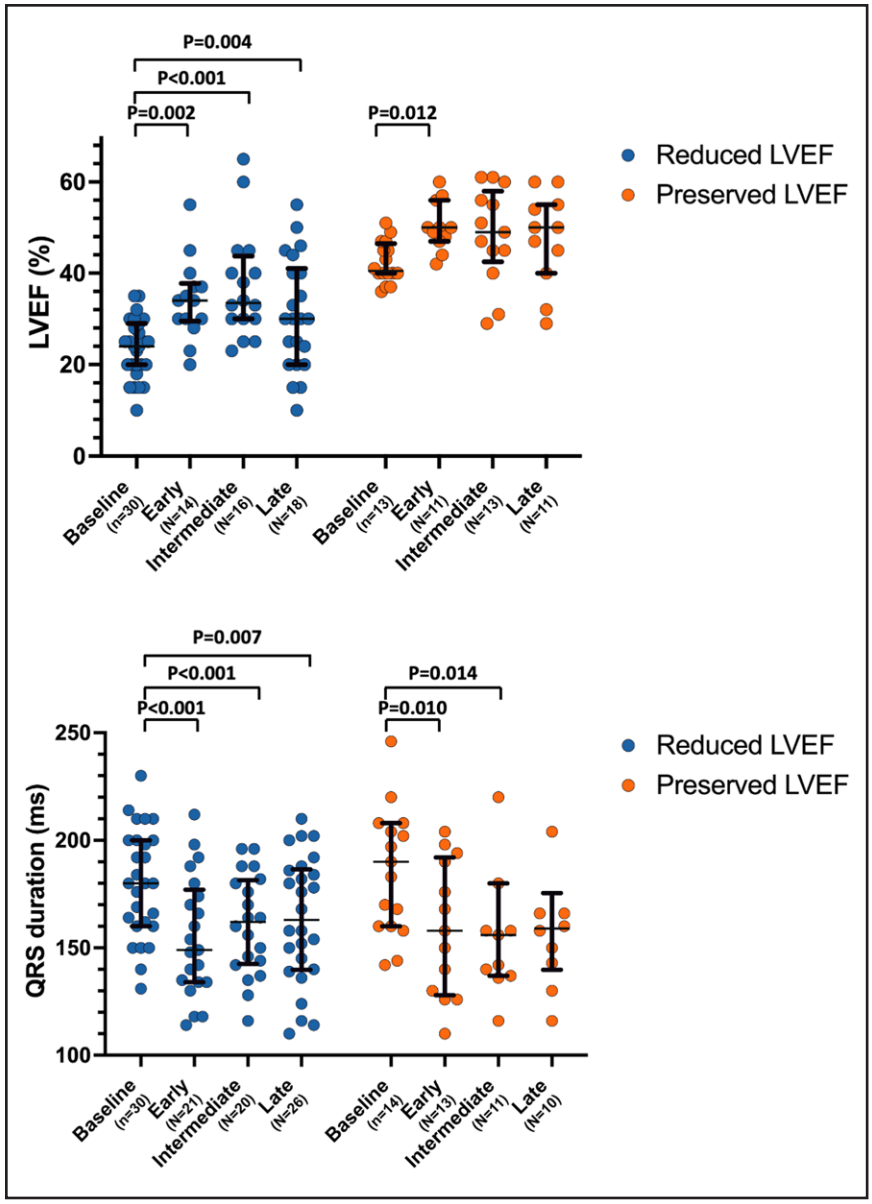

Figure 4. Functional outcomes in patients with preserved and reduced left ventricular ejection fraction (LVEF) at cardiac resynchronization therapy (CRT) implantation.
Scatter plots demonstrate the changes in LVEF and QRS duration in patients with reduced LVEF (≤35%) and preserved LVEF (>35%) at different time points, compared with baseline. Corrected *P* values are presented in the figure..

and late follow-up ($P \leq 0.004$). Initially, in patients with de novo CRT, LVEF increased from 29% [19%–44%] to 45% [30%–53%] and QRS duration decreased from 180 [160–208] to 150 [130–192] ms at early follow-up ($P=0.012$ and $P=0.005$, respectively). These early improvements were not sustained; LVEF and QRS duration no longer differed significantly from baseline ($P>0.05$) except in a small subset of patients who underwent de novo CRT (Table S3). At early, intermediate, and late follow-up, 44%, 50%, and 18% of the patients with de novo CRT had at least 10% increase in LVEF compared with baseline, respectively.

Both in patients with de novo and upgraded CRT, RVF improved at early and late follow-up. In patients with de novo CRT, 40% (n=5) of the patients had improved RVF at early follow-up and 75% (n=4) at late follow-up. In patients with upgraded CRT, a smaller proportion of patients had improvement in qualitative RVF. At early follow-up, 27% (n=11) of the patients had improved RVF and 43% (n=14) at late follow-up.

CRT in Subpopulations

Tables S4 and S7 describe the longitudinal outcomes in various subpopulations according to LV lead location, CRT indication, deceased, or transplanted patients, and QRS duration, respectively. Compared with a basal or apical LV lead position, LV leads positioned near the mid segments appeared to have more favorable outcomes with regards to LVEF and NYHA functional class. Patients who died or were transplanted had initially improved LVEF at early and intermediate follow-up, but not at late follow-up. In addition, they did not have shortening of QRS duration or lower NYHA functional class at any time points. Patients

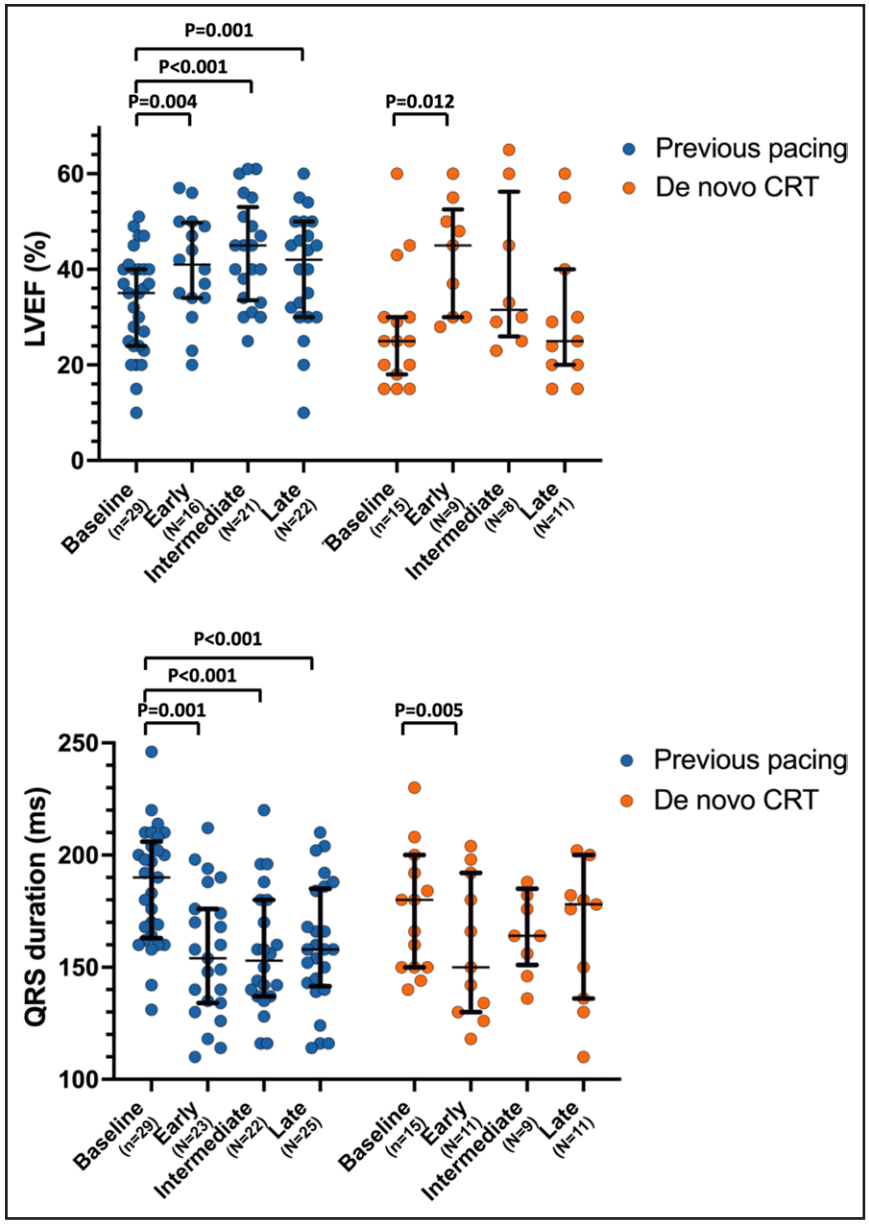

Figure 5. Functional outcomes in patients with upgraded cardiac resynchronization therapy (CRT) and de novo CRT.
Scatter plots demonstrate the changes in left ventricular ejection fraction (LVEF) and QRS duration in patients with previous right ventricular (RV) pacing and patients with de novo CRT at different time points, compared with baseline. Corrected *P* values are presented in the figure.

with shorter QRS duration (≤180 ms) at baseline had increased LVEF at various time points without improved NYHA functional class, although patients with longer QRS duration (>180 ms) experienced both LVEF and NYHA functional class improvement.

DISCUSSION

Key Findings

In this large retrospective, multicenter study, long-term CRT in patients with TOF was characterized by a shortening of QRS duration, increased LVEF, and improved NYHA functional class. Specifically, patients with prior RV pacing and reduced LVEF had consistent improvement in LVEF and NYHA functional class at all-time points. Even patients with preserved LVEF had evidence of shortened QRS duration with preservation of LVEF over time after CRT implantation. In contrast to CRT in setting of chronic RV pacing, de novo CRT appeared to be less favorable without persisting improvement in QRS duration and LVEF at follow-up. Overall, long-term survival was reasonable with a low rate of device-related complications.

Heart Failure in Patients With TOF

One of the leading causes of cardiovascular death in adult CHD is heart failure.[21] Not only do patients with TOF constitute the largest group of adults with repaired cyanotic CHD, they also comprise a substantial subset of patients with heart failure.[22,23] The prevalence of LV

heart failure is quickly growing in this population due to a co-existence of preoperative and intraoperative factors, long-term comorbidities, ventricular-ventricular interactions, and the availability of treatment modalities that are life-prolonging but not curative.[4,5] A recent multicenter study revealed that LV systolic dysfunction was present in 21% of 511 patients with repaired TOF.[4]

Over the decades after cardiac repair, patients with TOF can experience altered LV mechanical function related to maladaptive ventricular-ventricular interaction and pacing-induced remodeling. Such changes can lead to progressive ventricular dysfunction, ventricular arrhythmogenesis, and sudden cardiac death. Leftward shift of the ventricular septum, due to progressive RV volume overload and dysfunction, may induce abnormal strain patterns where septal insertion points meet the LV free wall.[24] This deleterious LV remodeling, although relatively unexplored, is thought to confer both prolonged and heterogeneous repolarization, slower conduction and fibrosis, and possibly localized impairment of the left bundle branch.[24,25] Together these adverse events conspire to create a complex substrate of electrical-mechanical dyssynchrony, which may be amenable to CRT.

Despite increased awareness of the prevalence of LV dysfunction, studies reporting on the use of CRT in patients with TOF are rare. While initial results are promising, studies have been characterized by a small sample size (n=8–14) and lack of granularity in quantifying CRT effect.[16–18] Interpretation of the (long-term) effect of CRT in patients with TOF has therefore been challenging, and more definitive evidence of benefit is warranted.

Upgrade versus de novo CRT

From a mechanistic point of view, CRT may be ineffective in patients with RBBB, unless there is an LV electromechanical delay. A subset of patients with RBBB who received an upgrade from previous RV pacing—which was the case in the majority of our patients—are likely to have electromechanical dysfunction underlying their LV systolic dysfunction due to the deleterious effects of RV pacing.[26] In this context, previous studies have shown nearly complete resolution of pacing-induced cardiomyopathy regardless of the extent of initial dysfunction.[26,27] Similarly, the current study shows that patients with previous RV pacing had reversal of LV dysfunction after CRT implantation. At early follow-up, LVEF increased from 36% [24%–44%] to 41% [34%–50%], with 38% of the patients showing ≥10% increase in LVEF, which persisted at late follow-up. Importantly, in patients without CHD, an increase of 10% or more in LVEF is associated with favorable clinical outcomes, with lower rates of death, heart transplantation, ventricular assist device implantation and hospitalization for heart failure.[28,29]

In contrast to patients who are upgraded to CRT, implantation of de novo CRT has been more controversial in patients with RBBB.[30] Multiple RCTs and meta-analysis have failed to show a clear benefit for the use of de novo CRT in this population, which is often attributed to the absence of LV electromechanical delay and a pacing-induced cardiomyopathy.[31–33] In the current study, patients with de novo CRT initially had a favorable response to CRT consisting of shortening of the QRS duration and improved LVEF. Although at intermediate and late follow-up, LVEF and QRS duration were no longer improved compared with baseline, a subgroup of patients had persisting improvement in LVEF and QRS duration. These findings are difficult to reconcile with the previous assertion that these patients do not possess some degree of LV electromechanical delay and suggest that specific patients with TOF and de novo CRT may benefit from resynchronization.

A substantially wide QRS may mask left bundle branch block (LBBB) in some repaired TOF patients receiving de novo CRT, which could serve as a therapeutic target for CRT in these patients. This atypical RBBB with superimposed delayed LV activation is previously described in non-CHD patients by Rosenbaum et al. as broad, slurred, sometimes bifid R wave on leads I and aVL, together with a leftward axis deviation.[34] In line with this, a subgroup of patients with RBBB have delayed lateral LV activation comparable to patients with LBBB.[35–37] Hara et al. further provided evidence that CRT may be beneficial in patients with RBBB if LV (electro-)mechanical delay is present.[38] In 40% of the patients with RBBB, LV mechanical delay was identified by speckle-tracking radial strain and these patients had improvement in LVEF, whereas those who lacked dyssynchrony had no significant changes in LVEF. Importantly, freedom from mortality, implantation of ventricular assist device and heart transplantation were more favorable in patients with RBBB and mechanical dyssynchrony in comparison to patients with RBBB and no dyssynchrony.[38]

These findings highlight the complexity and limitations of ECG to assess or predict CRT benefit. Multiple ECG criteria for predicting responders have been defined and are almost all subject to lack of consensus and poor inter-observer agreement.[39,40] In addition, in patients such as those with TOF, a variety of electrical activation patterns combined with functional and structural block in both ventricles can be concealed in the ECG, which further complicates clinical decision-making. Identifying these factors, and interpreting their interrelated meaning, is highly complex, especially in setting of a biventricular substrate.

RVF Improvement

In the current study, RVF significantly improved after implantation of CRT in 55% of patients at late follow-up. These results are in line with previous reported findings by Thambo et al, who evaluated the acute effects of

CRT on RVF in an animal model of RV dysfunction and dyssynchrony and in 8 symptomatic adults with repaired TOF. In this study, RVF improved in addition to LVF in both patients and animals.[41] We now show that RVF improvement was not restricted to patients with de novo CRT, and was also observed in patients with previous RV pacing. Although the results should be treated with caution due to the limited number of patients, these findings further emphasize the intricate relationship between RV and LV function.

In analogy to LV pacing in patients with LV failure and LBBB, targeted RV pacing can also significantly improve RVF. Especially in patients receiving de novo CRT, RVF improvement may also be subjective to lead position at the RV free wall, outflow tract, and synchronization to the RBBB over RV apex pacing.[42–46] Unfortunately, lead positioning and programming were not standardized among centers, which hindered comparisons in the current study.

Survival Rates With CRT

Despite the acknowledgment that the effects of CRT are likely variable among different types of CHD, dedicated studies on the long-term survival in the CHD population have been limited to patients with systemic right ventricular circulation and Fontan physiology.[12,47–51] Survival data from various CHD population with CRT have reported 5-year survival rates up to 80%, which is in accordance with the findings in the current study (79%).[47–51] Patients with TOF may, therefore, represent another large CHD group amenable to CRT with reasonable long-term outcomes.

Patients with TOF constitute the largest subgroup of implantable cardioverter defibrillator recipients in adults with CHD.[52] In setting of primary and secondary prevention, defibrillator function in patients with CRT may have impacted event-driven outcomes related to ventricular tachycardia and sudden cardiac death.[53] Especially in the current study, implantable cardioverter defibrillator therapy may play an important role as heart failure and ventricular tachycardia frequently coexist, and LV dysfunction appears to compound the risk for sudden cardiac death.[54] However, to some extent, CRT may reduce the risk for ventricular tachycardia and sudden cardiac death through reverse LV remodeling, unlike implantable cardioverter defibrillator, which is not a disease-modifying therapy.[55] Importantly, the incremental benefit of CRT-D over CRT alone is also unknown in non-CHD patients with heart failure due to the absence of randomized data directly assessing the differences between both treatments.

In recognition of specific anatomy, individual patterns of mechanical dyssynchrony and pacemaker-attributable risks, attempts have been made to further optimize outcomes of ventricular pacing in CHD. Predictors for mortality heart transplantation or heart failure hospitalization could not be identified, although the study was not powered for this purpose. Several other studies have identified risk factors in other (non-)CHD populations, such as apical lead positioning, endocardial systems, poor baseline systemic ventricular function, and traditional cardiovascular risk factors.[47,48,51,56,57] Various studies have also explored a more personalized approach in different CHD populations by tailoring lead positioning, preservation of physiological activation (by conduction system pacing) and pacemaker programming (pacing modalities and AV delays).[46,56,58] Patients with TOF and CRT may also benefit from this personalized approach due to a variability in surgical lesions, different levels of right (and left) bundle branch block and heterogeneous global RV and LV remodeling.[16,59]

Limitations

Due to the retrospective nature of this multicenter study, there were missing data for several parameters. These data were missing completely at random and not related to specific clinical baseline characteristics (Tables S8 through S11). In the current study, various factors have contributed to the missing data. Inherent to all retrospective multicenter studies is the challenge in collecting comprehensive data at times points that were determined in retrospect (in contrast to prospective registries). Moreover, several CRT systems were implanted more than a decade ago which predated current electronic medical records and digital image library, and thus precluding our ability to perform review of ECGs and echocardiograms in some of these cases. In addition, several patients were followed up at their district hospital. The inherent limitations in observational cohort studies apply also in this study, and causal associations cannot be claimed. Advanced imaging modalities and functional capacity assessment, such as 6-minute walk test, were often either unavailable or not routinely performed. Varied practice patterns among centers (spanning different time periods) resulted in lack of standardized CRT implantation and congestive heart failure treatment, which may have contributed to interpatient variability in response to CRT. Absence of uniform follow-up, concomitant or post-CRT cardiac surgery or interventions, and acquired comorbidities such as arrhythmias may have also impacted individual outcomes. Due to the current retrospective registry substudy design, it was not feasible to perform a head-to-head comparison with a matched control group. Future large prospective registries with a control group are necessary to overcome these limitations, and determine clinical gain from CRT, and discern subgroups who are most likely to derive long-term benefits.

Conclusions

In patients with TOF treated with CRT consistent improvement in QRS duration, LVEF, NYHA functional class, and

reasonable long-term survival were observed. The findings from this multicenter study support the consideration of CRT in this unique population. However, future large prospective studies are necessary to further assess the impact of CRT on clear clinical end points, identify (modifiable) risk factors, and evaluate the use of alternative pacing strategies to further optimize outcomes.

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Disclosures

None.

Supplemental Material

Tables S1–S11

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