ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 3109–3118
Published online 13 August 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12940

ORIGINAL RESEARCH ARTICLE

Cardiac resynchronization therapy in New York Heart Association class-IV patients dependent on intravenous drugs or invasive supportive treatments

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Abstract

Aims We sought to evaluate the effectiveness of cardiac resynchronization therapy (CRT) in far-advanced heart failure (FA-HF) patients with New York Heart Association (NYHA) class-IV status and dependency on intravenous drugs (IVDs) and/or invasive supportive treatments (ISTs).

Methods and results Among 305 patients who underwent CRT implantation between October 2005 to December 2019, we identified 17 FA-HF patients with NYHA class-IV status and dependency on IVDs (inotropes, diuretics, vasopressors, or vasodilators) and/or ISTs (extracorporeal membranous oxygenator or continuous renal replacement therapy). All patients (median age = 68.7 years, non-ischaemic cardiomyopathy = 15) remained dependent on several IVDs (2.2 ± 1.3 per patient) and/or ISTs for 11.3 ± 7.8 days due to multiple tapering failure (4.3 ± 3.2 per patient) before CRT implantation. However, 14 (82%) patients were successfully weaned from IVDs/ISTs within 5.2 ± 5.3 days following CRT, and 12 (71%) stayed alive for more than 1 year free of ventricular assist device or heart transplantation with symptom improvement (≥1 NYHA class) and a reduced annual HF hospitalization rate (P = 0.002). Considerable improvements in ventricular systolic function (P = 0.004) and volumetric reverse remodelling (P = 0.007) were noticed during the long-term follow-up period (35 ± 15 months post-CRT). The ventricular assist device/heart transplantation/death-free survival rate post-CRT was 71% and 65% at 1 and 3 years, respectively.

Conclusions Cardiac resynchronization therapy implantation may be a feasible treatment that can offer short-term and long-term clinical benefits for NYHA class-IV FA-HF patients who are dependent on IVDs/ISTs. When considering treatment options, CRT should not be prematurely excluded solely based on a patient's dependency on IVDs/ISTs without first attempting to identify favourable CRT response factors.

Keywords Cardiac resynchronization therapy; Far-advanced heart failure; New York Heart Association class IV; Prognosis

Received: 3 April 2020; Revised: 3 June 2020; Accepted: 19 July 2020
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Introduction

Cardiac resynchronization therapy (CRT) is a well-validated treatment to decrease mortality and hospitalization among patients with mild-to-moderate heart failure (HF).[1–3] However, the vast majority of prior research supporting the effectiveness of CRT has precluded patients with far-advanced HF symptoms of New York Heart Association (NYHA) functional class IV, particularly when they are dependent on intravenous drugs (IVDs) and/or other invasive supportive treatments (ISTs). For this reason, current guidelines do not recommend CRT implantation for such patients with far-advanced NYHA class-IV HF (FA-IV HF) who are dependent on IVDs/ISTs.[4,5] Although ventricular assist devices (VADs) or heart transplantation (HT) may be an alternative option for this patient population, not all patients can benefit from such forms of

treatment, and these options might not be indicated or feasible due to various comorbidities that frequently occur in FA-IV HF patients.

Recently, several studies have documented a relatively short-term clinical benefit of CRT in this patient population, although the response rates were not as high as those of patients with less severe HF.[6–12] We hypothesized that CRT would provide beneficial effects even for some selected FA-IV HF patients. Accordingly, we sought to evaluate the short-term and long-term effectiveness of CRT among FA-IV HF patients in terms of echocardiographic as well as clinical responses and to identify the predictors of CRT response in this patient group.

Methods

Study population

Demographic, clinical, and CRT-related parameters in conjunction with electrocardiograms (ECGs) and echocardiographic data for all patients undergoing CRT implantation at our institution were entered prospectively into our CRT registry. From October 2005 to December 2019, 305 CRT procedures were performed. In the registry, we carefully searched for patients with FA-IV HF, which was defined when all the following criteria were met without any of the exclusion criteria: (i) ongoing resting dyspnoea; (ii) dependent status on ≥1 IVDs (dobutamine, milrinone, dopamine, norepinephrine, epinephrine, furosemide, and nitroprusside) and/or various ISTs such as extracorporeal membranous oxygenator (ECMO), continuous renal replacement therapy (CRRT), or mechanical ventilator prior to, during, and after CRT procedure; and (iii) undergoing non-elective CRT procedures. We excluded elective CRT implantation or replacement procedures. Patients were also excluded when the IVDs/ISTs were weaned before CRT implantation. Dependency on IVDs/ISTs was defined as inability to withdraw IVDs/ISTs due to worsening of HF symptoms, haemodynamic instability, or aggravation of laboratory parameters. Tapering failure was defined as the need to re-escalate the level of support using IVDs/ISTs within 24 h following a tapering attempt. This study was conducted according to the principles of the Declaration of Helsinki. Approval for the present study was obtained from the institutional review board of our institute, and the requirement for written informed consent was waived.

Cardiac resynchronization therapy implantation and programming

All CRT devices were implanted transvenously using sterile techniques. The decision of whether to add a defibrillator to the CRT device was made at the physicians' discretion. The preferred sites for left ventricular (LV) lead implantation were the anterolateral, lateral, or posterolateral wall, and we were able to avoid LV apical pacing in all cases. After the procedure, atrioventricular (AV) node ablation was carried out when patients showed atrial fibrillation (AF) with a rapid ventricular response to maximize biventricular pacing percentage (BiV-p%).

The optimal AV and ventriculoventricular delays were determined when the greatest stroke volume on echocardiography or the narrowest QRS duration (QRSd) on 12-lead ECG was achieved before discharge. In patients with sinus rhythm, the CRT device was programmed in DDD(R) mode. In AF patients, the basal and maximal pacing rates were set at 60–75 beats per minute and around 80% of the age-predicted maximum heart rate under VVIR pacing mode, respectively.[13]

Electrocardiographic and echocardiographic data

QRS duration was measured before and after CRT implantation, and baseline QRS morphology was classified as either left bundle branch block (LBBB) or non-LBBB. The definition of LBBB needed to satisfy all of the following criteria: (i) QRSd ≥ 130 ms, (ii) QS or rS in leads V1 and V2, and (iii) mid-QRS notch or slurring in ≥2 contiguous leads (i.e. I, aVL, V1, V2, V5, or V6).[14] In patients who underwent upgrade procedures to CRT devices, paced QRSd was considered as baseline QRSd because they were almost completely dependent on ventricular pacing.

Two-dimensional echocardiographic assessment was performed using commercially available equipment (Vivid 7 or 9 from GE Healthcare, Chicago, IL, USA). The LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), LV ejection fraction (LVEF), and left atrial volume index were calculated by applying a modified biplane Simpson's method in apical four-chamber and two-chamber views according to standard guidelines.[15]

Short-term and long-term outcomes

To evaluate the acute response to CRT during hospitalization, we assessed immediate QRS narrowing, any change in NYHA class, and pre-CRT and post-CRT duration of IVD therapy or length of hospital stay. After discharge, clinical and device follow-up visits were performed for approximately 2 weeks and then every 3 months thereafter at our dedicated device clinic. NYHA class, chest X-ray, 12-lead ECGs, and BiV-p% reports were obtained at each clinic visit. The BiV-p% was calculated by averaging the values of the first three visits. Adjustments to CRT parameters including pacing rate, mode, and AV/ventriculoventricular delay were left to the physician's discretion during the follow-up period.

Long-term responses to CRT were evaluated using the 1-year clinical and echocardiographic response rates, change in annual HF-related hospitalization (HF hospitalization) rate, and overall and cardiac deaths. Any VAD implantation or HT procedures were also investigated. The 1-year clinical response was strictly defined only when all of the following conditions were met: (i) survival free of VAD/HT, (ii) improvement of ≥1 NYHA class, and (iii) decreased annual HF hospitalization rate (or no hospitalization) after CRT. To compare HF hospitalization rates, patient records 1 year prior to and 1 year after CRT implantations were examined. Echocardiographic improvement was assessed as relative changes in LVESV ($\frac{\text{preCRT} - \text{postCRT}}{\text{preCRT}} \times 100\%$) and LVEF compared with baseline. Patients with a relative reduction in LVESV of ≥15% and ≥30% were defined as regular and super responders, respectively.[16] All deaths were considered as cardiac related unless a definite non-cardiac cause could be identified. An HF hospitalization was defined according to the 2016 European Society of Cardiology guidelines following careful evaluation of HF symptoms or signs, chest radiography, cardiac dysfunction by echocardiography, and biomarkers.[5]

Statistical analysis

Continuous variables were described as median with interquartile range (IQR) or mean ± standard deviation. Differences were compared using unpaired *t*-test or Mann–Whitney *U* test depending on the normality of distribution as tested by the Shapiro–Wilk normality test. A paired *t*-test or Wilcoxon signed rank test was used to compare the pre-CRT and post-CRT ECG, and echocardiographic variables, duration of IVD therapy, N-terminal pro brain natriuretic peptide (NT-proBNP) levels, and annual HF hospitalization rate. Categorical data were presented as an absolute value with percentage, and any differences were analysed using Fisher's exact test or χ^2 test as appropriate. A survival test was performed using the Kaplan–Meier test, and differences were confirmed using the log-rank test. Results were considered statistically significant when the *P* value was <0.05. Statistical analyses were performed using R software, version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

Of our CRT registry, 17 patients were able to meet all the predefined criteria of FA-IV HF, and their baseline characteristics are presented in *Table 1*. The median (IQR) age was 68.7 (63.3–74.2) years, and the cause of HF was predominantly non-ischaemic cardiomyopathy (15/17, 88%) with only two patients having previously undergone coronary revascularization. The mean duration of HF treatment prior to CRT implantation was 4.6 ± 4.1 years. Despite optimal medical therapy (OPT), they suffered recurrent HF hospitalizations at a rate of 1.9 ± 1.4 times within 12 months before CRT implantation. All patients had severe LV systolic dysfunction with a median (IQR) LVEF of 20% (16–26). The QRSd was markedly prolonged with a median (IQR) value of 162 (146–182) ms. LBBB pattern was observed in 15 patients (88%). More than half of the patients (9/17, 53%) showed paroxysmal or persistent/permanent AF.

During the index hospitalization, all patients required multiple (2.2 ± 1.3 per patient) IVD therapy (*Table 1*). Despite several cautious attempts to taper the IVDs, all patients

Table 1 Baseline characteristics of study population

Demographics and medical history	(*n* = 17)
Age (years)	68.7 (63.3–74.2)
Male	11 (64.7)
Non-ischaemic cardiomyopathy	15 (88.2)
Paroxysmal/persistent or permanent AF	3 (17.6)/6 (35.3)
Hypertension	9 (52.9)
Diabetes mellitus	6 (35.3)
Chronic kidney disease	5 (29.4)
Pre-CRT hospital stay (days)	18 (9–22); 17.0 ± 9.7
Intravenous drugs[a] or invasive supportive treatment, pre-CRT	
Inotropes	13 (76.5)
Diuretics	13 (76.5)
Vasodilators	1 (5.8)
Vasopressors	5 (29.4)
Number of intravenous drugs per patient	2 (1–3); 2.2 ± 1.3
Total duration ≥1 intravenous drug (days)	10 (3–17); 11.3 ± 7.8
Number of tapering failure per patient	3 (3–6); 4.3 ± 3.2
ECMO/CRRT	1 (5.8)/3 (17.6)
Electrocardiographic parameters	
Heart rate (beat per minute)	83 (78–85)
Intrinsic QRS duration (ms)	162 (146–182)
Corrected QT (ms)	513 (492–545)
LBBB morphology	15 (88.2)
Echocardiographic parameters	
LVEF (%)	20 (16–26)
LVEDV (mL)	271 (223–294)
LVESV (mL)	200 (178–250)
MR ≥ moderate/TR ≥ moderate	7 (41.2)/4 (23.5)
Procedure or device-related data	
De novo/upgrade	14 (82.4)/3 (17.6)
CRT-D/CRT-P	15 (88.2)/2 (11.8)
LV lead pacing site	
Lateral/non-lateral in LAO view	17 (100)/0 (0)
Apical/non-apical in RAO view	0 (0)/17 (100)
RV lead in apical position	3 (17.6)
Biventricular pacing percentage (%)	99 (94–99); 97.3 ± 5.7

AF, atrial fibrillation; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillator; CRT-P, CRT-pacemaker; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membranous oxygenator; LAO, left anterior oblique; LBBB, left bundle branch block; LV, left ventricle; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; RAO, right anterior oblique; RV, right ventricle; TR, tricuspid regurgitation.
Values are expressed as *n* (%), median (interquartile range), or mean with standard deviation.
[a]Intravenous drugs included inotropes (dobutamine, milrinone, dopamine), vasopressors (norepinephrine, epinephrine), diuretics (furosemide), and vasodilators (nitroprusside).

remained dependent on at least one IVD for 11.3 ± 7.8 days before CRT implantation; the median (IQR) number of tapering failures of IVDs was 3 (3−6). NT-proBNP levels were measured in 16 of 17 patients with the median (IQR) value of 9403 (2906–20 744) pg/mL prior to CRT implantation. Detailed information on the IVDs and pre-CRT oral medications are presented in Supporting Information, *Tables S1* and *S2*. In addition, CRRT was required in three patients for severe renal insufficiency and ECMO support in one patient to manage shock. On the day of CRT implantation, the systolic (98 ± 12 mmHg) and diastolic (64 ± 10 mmHg) blood pressures were low despite multiple supportive managements.

Acute response to cardiac resynchronization therapy

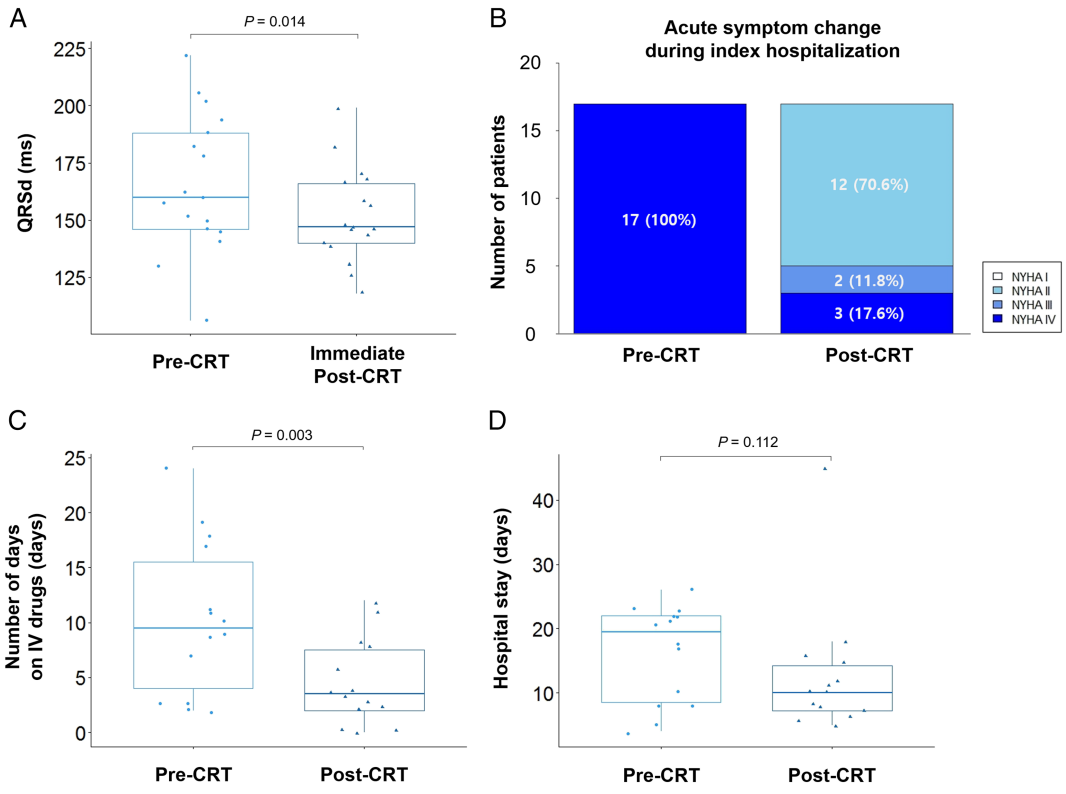
All CRT procedures were successfully completed without significant procedure-related complications. After the procedure, all but three patients demonstrated significant QRS narrowing from 162 to 147 ms, $P = 0.014$ (*Figure 1A*). Fourteen (82.4%) patients showed immediate symptom improvement (*Figure 1B*). Therefore, these 14 patients were successfully weaned from IVDs within 3.5 (IQR, 1.5–8.0) days following the CRT procedure, and they were eventually discharged alive within an additional 4.5 (IQR, 3.0–8.0) days after weaning from all IVDs/ISTs. Accordingly, the post-CRT duration of IVD therapy [3.5 (1.5–8.0) days] was markedly reduced compared with the pre-CRT value [9.5 (7.0–17.3) days] among the 14 survivors ($P = 0.003$) (*Figure 1C*). In addition, there was a clear trend towards a decrease in the length of hospital stay: 19.5 (8.0–22.3) vs. 10.0 (6.8–15.3) days, $P = 0.112$ (*Figure 1D*). However, three (17.6%) patients remained dependent on IVD therapy without symptom improvement and died from HF aggravation (post-CRT days 5, 14, and 17, respectively) during the hospitalization.

Long-term response to cardiac resynchronization therapy

One-year clinical response

Two of the 14 survivors (14.3%) regressed to FA-IV HF status during the follow-up period; one underwent HT at 3 months post-CRT, and the other died of HF aggravation 12 months post-CRT. However, symptom improvement was well maintained in the remaining 12 patients (12/14, 85.7%) during the first year after CRT. In fact, further improvement in HF

Figure 1 Acute response to CRT. (A) Change of QRS duration, (B) symptom change during index hospitalization, (C) change in the duration of IVdrug use, and (D) change in the duration of hospital stay. CRT, cardiac resynchronization therapy; IV, intravenous; NYHA, New York Heart Association; QRSd, QRS duration.



DOI: 10.1002/ehf2.12940

symptoms was observed in four patients up to NYHA class I (*Table 2*). In line with symptom improvement, the HF hospitalization rate was dramatically reduced during the first year post-CRT compared with the last year pre-CRT (1.7 ± 1.3 vs. 0.3 ± 0.6 per patient, $P = 0.002$) (*Figure 2A*). Additionally, compared with the baseline value, the median (IQR) NT-proBNP level significantly decreased during the follow-up period (median, 183 days; IQR 75–425 days) after CRT: 7562 (2906–13 948) vs. 2304 (1457–3865) pg/mL, $P = 0.002$.

Overall, 12 of 17 (70.6%) patients remained alive without VAD/HT for 1 year after CRT and satisfied all of our 1-year clinical responder criteria. Notably, 10 of the 12 clinical responders (83.3%) showed no HF hospitalizations during the first year after CRT.

Echocardiographic response

One-year follow-up echocardiography performed in the 12 clinical responders revealed a significant improvement in LVEF ($P = 0.011$) (*Figure 2B*). The LVEDV and LVESV were likely to decrease at 12 months compared with baseline values (*Figures 2C* and *2D*). Of the 1-year clinical responders, eight were also identified as echocardiographic responders (LVESV reduction $\geq$ 15%), while three showed echocardiographic super responses (LVESV reduction $\geq$ 30%) at 12 months post-CRT (*Table 2*). Moreover, the echocardiographic response became more prominent at the last echocardiographic evaluation (35 ± 15 months post-CRT), especially in regard to LVEF [19% (15−24) vs. 31% (26–45), $P = 0.004$] and LVESV [220 (181–258) vs. 134 (100–224) mL, $P = 0.007$] (*Figures 2B* and *2D*).

Long-term survival

During the entire follow-up period (44.7 ± 38.4 months), there were six cardiac deaths, one cancer-related death, one HT, and no VAD procedures. The VAD/HT/death-free survival rate was 77%, 71%, and 65% at 6 months, 1 year, and 3 years, respectively (*Figure 3A*). One-year clinical responders ($n = 12$) showed a better long-term prognosis compared with non-responders ($n = 5$) ($P < 0.001$) (*Figure 3B*).

One-year clinical responders vs. non-responders

In regard to baseline characteristics, 1-year clinical responders were more likely to have LBBB morphology compared with non-responders: 12 (100%) vs. 3 (60%), $P = 0.132$ (*Table 3*). Pre-CRT QRSd was significantly greater in responders than in non-responders: 173 (160–198) vs. 146 (145–150) ms, $P = 0.027$. In addition, immediate QRS narrowing was more pronounced in the responders than in the non-responders: 20 (9–34) vs. 4 (2–24) ms, $P = 0.048$.

Discussion

Main findings and merits of the present study

The main findings of the present study were that both short-term and long-term beneficial effects of CRT were observed even in patients with FA-IV HF who remained dependent on IVDs/ISTs. More than 80% of patients (14/17, 82.4%) were successfully weaned off IVDs/ISTs, experienced immediate symptom improvement following CRT, and survived to discharge. Duration of IVD therapy was markedly reduced during the post-CRT period compared with pre-CRT phases. About two-thirds of patients (12/17, 70.6%) satisfied all of the 1-year clinical responder criteria: (i) staying alive ≥1 year without VAD/HT, (ii) symptom improvement ≥1 NYHA class, and (iii) reduced or zero annual HF hospitalization rate. In addition, long-term echocardiographic improvement was clearly observed in terms of changes in LVEF and LVESV. Overall, the VAD/HT-free survival rate was 71% at 1 year and 65% at 3 years after CRT.

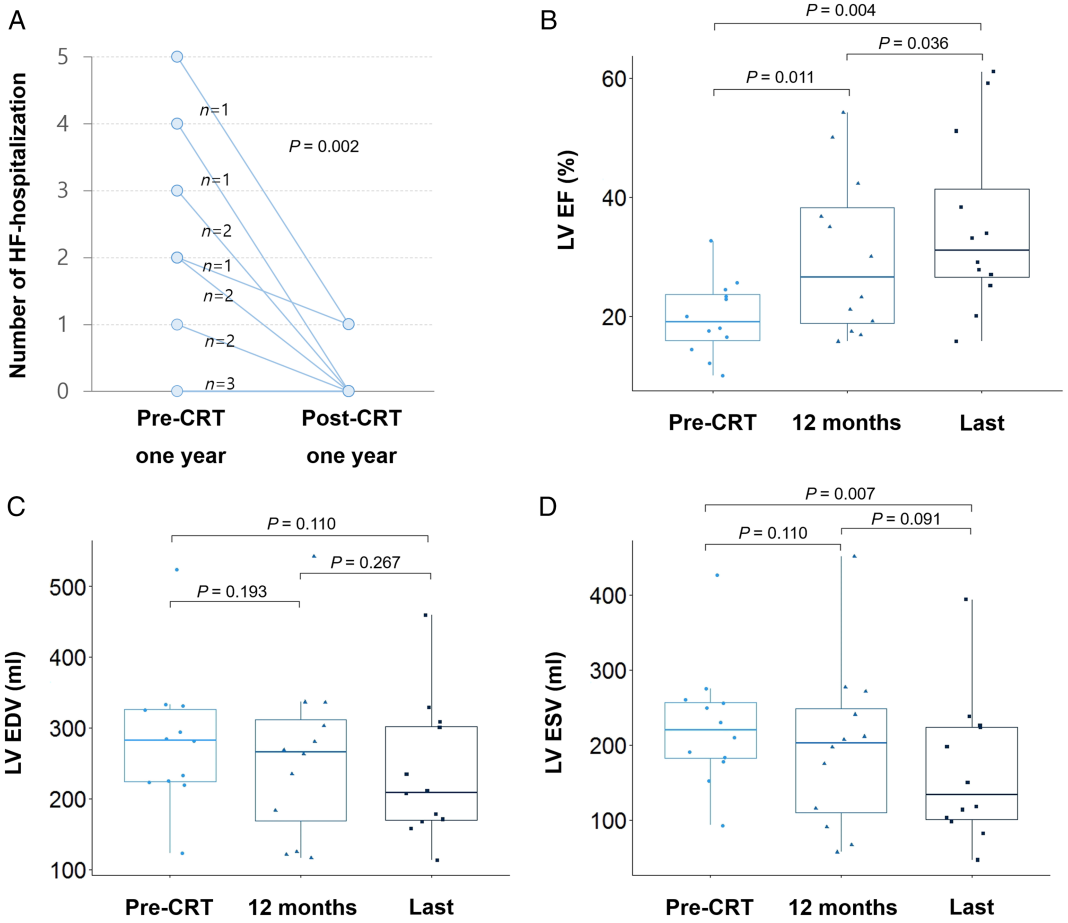
Although several studies have tried to evaluate the efficacy of CRT in this patient population, the current study offers several merits over the previous ones.[6–12,17–20] First, our study population, which was composed only of FA-IV HF patients, was more homogeneous than others[17–20]; in a previous investigation, only one-third of patients exhibited NYHA class-IV symptoms.[19] In other studies, more than half of the patients did not receive IVDs during CRT implantation, which

Table 2 Improvement in symptom, hospitalization rate, and ventricular function at 1 year after CRT

Symptom improvement	≥1 NYHA class at 12 months	12/17 (71%)
	≥2 NYHA class at 12 months	9/17 (53%)
	NYHA class I status at 12 months	4/17 (24%)
Hospitalization rate for 1 year after CRT	No HF hospitalization	10/17 (59%)
	Decreased annual HF hospitalization	2/17 (12%)
	No or decreased annual hospitalization	12/17 (71%)
Ventricular systolic function	Reduction in LVESV ≥ 15%	8/17 (47%)
	Reduction in LVESV ≥ 30%	3/17 (18%)
Predefined 1-year clinical response[a]	Survival status, ≥1 NYHA improvement, and no or decreased HF hospitalization for 1 year after CRT	12/17 (71%)

CRT, cardiac resynchronization therapy; LVESV, left ventricular end-systolic volume; NYHA, New York Heart Association.
[a]One-year clinical response was defined when patients met all of the following criteria including survival status free of ventricular assist device or heart transplantation at least 12 months post-CRT, symptom improvement ≥1 NYHA class, and reduced annual heart failure hospitalization rate (or no heart failure hospitalization).

Figure 2 Long-term response to CRT. (A) Change in the annual HF hospitalization in patients who satisfied 1-year clinical response; (B) change in LVEF before CRT implantation, at 12 months after CRT implantation, and at the last visit; (C) change in LVEDV before CRT implantation, at 12 months after CRT implantation, and at the last visit; and (D) change in LVESV before CRT implantation, at 12 months after CRT implantation, and at the last visit. CRT, cardiac resynchronization therapy; HF, heart failure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

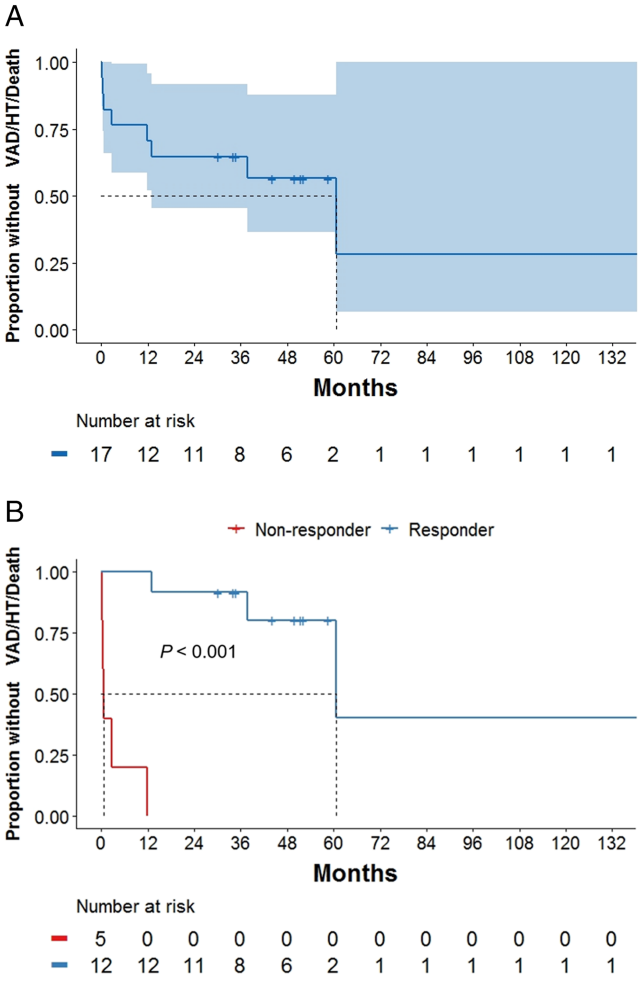


increased the heterogeneity of their study population.[17,18] However, all patients in our study who experienced repeated HF hospitalizations and multiple episodes of tapering failure of IVDs/ISTs remained dependent on IVDs/ISTs before, during, and immediately after CRT implantation. Second, we used a more rigorous definition of clinical response by requiring a survival status free of VAD/HT, a decrease in HF hospitalization rate, and improvement in NYHA class. Previous studies have defined a clinical response as a change in NYHA class alone, but this method is prone to errors due to the possibility for subjective decisions. Lastly, we also provided the longest echocardiographic (35 ± 15 months post-CRT) and clinical (44.7 ± 38.4 months) follow-up data following CRT in this sickest patient group. In some previous studies, the clinical follow-up period was relatively short.[6,8,17,19] In addition, data on the echocardiographic response were not presented[6,9,10,12,17–19] or may only have been collected during a very short (1–3 months) period,[8,11] which was likely related to the lack of significant echocardiographic reverse remodelling in their results. Contrastingly, in our data, an echocardiographic response was definite after long-term BiV pacing therapy.

Prognosis of ambulatory New York Heart Association class-IV heart failure patients without cardiac resynchronization therapy

To better understand the efficacy of CRT for FA-IV HF patients, one of the sickest groups, it would be informative to review the natural course of less severe HF patients who have not undergone CRT implantation. NYHA class-IV patients (n = 217, mean QRSd of 161 ms) who enrolled in the control (OPT) arm of Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trials were more likely to have less severe HF than our patients because they were all

Figure 3 Long-term VAD/HT/death-free survival curve. (A) VAD/HT/death-free survival in all patients and (B) comparison of responder and non-responder. HT, heart transplantation; VAD, ventricular assist device.



ambulatory and not dependent on IVDs/ISTs.[21] However, at the 1-year follow-up evaluation, the overall survival rate of the OPT arm without CRT implantation was only 56%. Similarly, the 1-year survival rate without CRT was 50–70% in ambulatory classes III–IV HF patients with QRS widening (≥120 ms, *n* = 2720) from the Swedish Heart Failure Registry.[22] Patients with QRS widening or dependency on IVDs/ISTs, like our patients, usually experience a worse prognosis than those without.[23,24]

Outcomes of cardiac resynchronization therapy for intravenous drug/invasive supportive treatment-dependent far-advanced New York Heart Association class-IV heart failure patients

In a retrospective analysis of 112 stage-D HF patients dependent on a chronic infusion of dobutamine or milrinone, the overall survival rate was just 24% during a median follow-up of 130 days, although QRSd and eligibility for CRT were not evaluated.[25]

Recently, several studies have shown that CRT did improve HF symptoms and survival rates of some IVD-supported HF patients with FA-IV status, although the overall outcomes were not as good as in HF patients with less disease severity; 1-year survival ranged from 40% to 80%.[6–12,17,26,27] A beneficial effect of rescue CRT implantation for inotrope-dependent HF patients was also demonstrated in a recently published meta-analysis that incorporated 151 patients from eight related studies.[20] The success rate for weaning from IVDs was 93%, and the overall 1-year survival rate was 69% after CRT in their pooled analysis. In line with these previous studies, our CRT patients showed successful weaning from IVDs/ISTs in 82%, and the 1-year clinical response was 71%. These results are acceptable considering that clinical outcomes were very poor in NYHA class-IV patients without CRT even if they were not dependent on IVDs/ISTs and were even worse when they were dependent.

Table 3 Comparison of the non-responder and responder groups

	Non-responder (n = 5)	Responder (n = 12)	P value
Age (year)	63 (55–81)	69 (64–73)	0.527
Male, n (%)	2 (40.0)	9 (75.0)	0.413
Non-ICM, n (%)	4 (80.0)	11 (91.7)	1.000
Hypertension, n (%)	2 (40.0)	7 (58.3)	0.875
Diabetes mellitus, n (%)	1 (20.0)	5 (41.7)	0.768
Chronic kidney disease, n (%)	2 (40.0)	3 (25.0)	0.973
AF, n (%)	2 (40.0)	7 (58.3)	0.875
LBBB, n (%)	3 (60.0)	12 (100)	0.132
Pre-CRT QRS duration (ms)	146 (145–150)	173 (160–198)	0.027
Post-CRT QRS duration (ms)	146 (143–146)	152 (139–168)	0.673
Immediate QRS narrowing (ms)	4 (2–24)	20 (9–34)	0.048
LVEF (%)	26 (20–28)	19 (15–24)	0.206
LVEDV (mL)	225 (158–271)	283 (228–328)	0.279
LVESV (mL)	152 (118–200)	220 (181–258)	0.160
LAVI (mL/m^2)	66 (61–69)	84 (64–91)	0.268

AF, atrial fibrillation; ICM, ischaemic cardiomyopathy; LAVI, left atrial volume index; LBBB, left bundle branch block; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume.

Clinical implications

Given the worst natural course of IVD/IST-dependent FA-IV HF patients, additional therapeutic modalities must be considered for this patient population, such as VAD, HT, or CRT. However, as already mentioned, donor hearts are not always available at opportune times, and HT might not be indicated due to various comorbidities. Even in the latest version of CF-VAD, rates of VAD-related complications, including stroke, device infection, bleeding, right HF, and VAD malfunction, are still reported to be as high as 40%.[28,29] Therefore, CRT must first be considered prior to left VAD or HT as a feasible treatment option, especially when super response factors are present. Indeed, all of our patients had very poor baseline characteristics compared with those enrolled in the VAD studies.[23] Nevertheless, weaning from IVDs/ISTs became possible after CRT implantation; 11 of 17 patients were no longer hospitalized for HF aggravation, and 47% of patients showed echocardiographic response after CRT. In one patient, weaning from CRRT and ECMO was possible after CRT, and LVEF improved from 26% to 54% after 7 months of follow-up.[27] Another patient was able to stay alive with a CRT device for 3 months and then received a successful HT. Therefore, CRT can function as a good bridge therapy connecting patients to more fundamental treatments.

It is vital to define favourable CRT response factors in this patient group because the overall response rate is not as high in less severe HF groups. However, small sample sizes of previous studies and our cohort make it difficult to identify predictors of a better CRT response. These predictors may not be significantly different from super response factors already identified in previous studies, which include non-ischaemic cardiomyopathy, LBBB morphology, QRSd $>$ 150 ms, female gender, and so on.[30] Indeed, all our patients with a 1-year clinical response had non-ischaemic cardiomyopathy, LBBB, and QRSd $>$ 160 ms. Furthermore, the 1-year clinical responders showed longer QRSd than non-responders: 173 (160–198) vs. 146 (145–150) ms, P = 0.027. In a study that predominantly included patients with ischaemic cardiomyopathy, the 1-year survival tended to decrease below 50%.[26] The 1-year survival rate was also affected by proportion of LBBB patients[7,9,10,12,19]; it was only 40% when the proportion of LBBB patients was $<$50%, but it increased to 80% if LBBB patients numbered $>$70%.

Limitations

The present study had several limitations inherent to its retrospective design and small sample size. Additionally, there was no control group of patients who had not undergone CRT implantation to compare with the test group. Therefore, we acknowledge that no definite conclusions should be drawn based on the present results. However, sample sizes in previous studies were all $<$30, and it would not be easy to perform a randomized controlled trial in this sickest patient group. We were unable to perform a multivariate analysis to identify predictors for a CRT response due to the limited number of patients. Therefore, prospective observation studies on a larger scale are needed to validate the efficacy of CRT implantation for FA-IV HF patients. In our patient cohort, we did not measure high-sensitivity troponin T, a useful biomarker with prognostic significance in various cardiovascular diseases such as HF, post-operative cardiogenic shock, coronary artery diseases, and valvular heart diseases.[31,32]

Conclusions

Short-term and long-term beneficial effects of CRT were observed even in FA-IV HF patients who were dependent on

DOI: 10.1002/ehf2.12940

IVDs/ISTs. About 82% of patients were successfully weaned from IVDs/ISTs, and 70% stayed alive for more than 1 year free of VAD/HT with symptom improvement and a reduced annual HF hospitalization rate. Echocardiographic reverse remodelling also became more definite during the long-term follow-up period. Accordingly, a patient's dependency on IVDs/ISTs should not deter physicians from considering the option of CRT without first attempting to identify favourable CRT response factors.

Supporting information

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

Table S1. Details on intravenous drugs used before and after CRT implantation.
Table S2. Pre-CRT oral medications.

Conflict of interest

None declared.

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