



Clinical outcome of cardiac resynchronization therapy in dilated-phase hypertrophic cardiomyopathy

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Abstract

Backgrounds Clinical trials have demonstrated that cardiac resynchronization therapy (CRT) is effective in patients with “non-ischemic cardiomyopathy”. However, patients with dilated-phase hypertrophic cardiomyopathy (DHCM) have been generally excluded from such trials. We aimed to compare the clinical outcome of CRT in patients with DHCM, idiopathic dilated cardiomyopathy (IDCM), or ischemic cardiomyopathy (ICM). **Methods** A total of 312 consecutive patients (DHCM: $n = 16$; IDCM: $n = 231$; ICM: $n = 65$) undergoing CRT in Fuwai hospital were studied respectively. Response to CRT was defined as reduction in left ventricular end-systolic volume (LVESV) $\geq 15\%$ at 6-month follow-up. **Results** Compared with DHCM, IDCM was associated with a lower total mortality (HR: 0.35, 95% CI: 0.13–0.90), cardiac mortality (HR: 0.29; 95% CI: 0.11–0.77), and total mortality or heart failure (HF) hospitalizations (HR: 0.34, 95% CI: 0.17–0.69), independent of known confounders. Compared with DHCM, the total mortality, cardiac mortality and total mortality or HF hospitalizations favored ICM but were not statistically significant (HR: 0.59, 95% CI: 0.22–1.61; HR: 0.59, 95% CI: 0.21–1.63; HR: 0.54, 95% CI: 0.26–1.15; respectively). Response rate to CRT was lower in the DHCM group than the other two groups although the differences didn’t reach statistical significance. **Conclusions** Compared with IDCM, DHCM was associated with a worse outcome after CRT. The clinical outcome of DHCM patients receiving CRT was similar to or even worse than that of ICM patients. These indicate that DHCM behaves very differently after CRT.

J Geriatr Cardiol 2017; 14: 238–244. doi:10.11909/j.issn.1671-5411.2017.04.002

Keywords: Cardiac resynchronization therapy; Dilated-phase hypertrophic cardiomyopathy; Idiopathic dilated cardiomyopathy; Ischemic cardiomyopathy

1 Introduction

Cardiac resynchronization therapy (CRT) is an established therapy for patients with severely impaired left ventricular (LV) systolic function and evidence of ventricular dyssynchrony.^[1,2] It is generally accepted that the response to CRT is variable and partly determined by the etiology of the underlying cardiomyopathy. Previous studies have shown that ischemic cardiomyopathy (ICM) is associated with a worse outcome than non-ischemic cardiomyopathy (NICM).^[3,4] However, NICM encompasses a broad range of

cardiomyopathies, including the idiopathic dilated cardiomyopathies (IDCM), hypertensive cardiomyopathy, cardiomyopathies of valvular origin and Dilated-phase hypertrophic cardiomyopathy (DHCM). While CRT has been proved to be effective in unselected patients with ‘NICM’, the effects of CRT in patients with DHCM have not been specifically addressed.

Over the past 10 to 20 years, systematic utilization of the implantable cardioverter defibrillator (ICD) to prevent sudden death has altered the clinical course for many high-risk hypertrophic cardiomyopathy (HCM) patients. As a consequence, the epidemiology of HCM-related mortality is evolving, with DHCM emerging as a more major component of the disease spectrum than previously regarded.^[5] Actually, these selected patients with DHCM are receiving CRT in “real world” practice.

In this study, we assess the long-term clinical outcome of CRT in selected patients with DHCM and compare them with patients with IDCM or ICM.

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Received: January 20, 2017 **Revised:** March 12, 2017

Accepted: April 7, 2017 **Published online:** April 28, 2017

2 Methods

Patients with DHCM ($n = 16$), IDCM ($n = 231$), or ICM ($n = 65$) undergoing CRT were recruited from a single centre (Fuwai Hospital, Beijing, China) between March 2001 to January 2016. DHCM was defined as LV systolic dysfunction [left ventricular ejection fraction (LVEF) $< 50\%$] in the presence of (1) unexplained LV hypertrophy or (2) previous documentation of unexplained LV hypertrophy on echocardiography, or (3) proven familial HCM with at least one relative who had an unequivocal diagnosis. The diagnosis of the ICM was based on LV systolic dysfunction and a clinical history of prior myocardial infarction, prior percutaneous coronary intervention, or prior coronary bypass surgery, or evidence of clinically significant coronary stenosis (at least 75% narrowing of at least one of the three major coronary arteries), similarly to the assignment used in large CRT trials.^[6] IDCM was diagnosed when the patients were found to have LV systolic dysfunction in the absence of any other known cardiac disease.^[7] The patients were excluded if LV dysfunction was secondary to one of the following: hypertension ($> 160/100$ mmHg), history of alcohol abuse (> 100 g alcohol/day), tachycardia-induced cardiomyopathy, Cor pulmonale, diseases of pericardium, or congenital heart diseases. This study conforms to the Declaration of Helsinki. All patients gave written informed consent, and the study was approved by the local Ethics Committees.

2.1 Device therapy

Technical aspects of leads and device implantation were described in detail previously.^[8] Briefly, the coronary sinus (CS) was cannulated from left subclavian and/or cephalic entry site using a commercially available long peelable guiding sheath. The LV lead was positioned in the venous system, preferably in the lateral or posterolateral vein. The right atrial (RA) and right ventricular (RV) leads were placed regularly at the RA appendage and the RV apex. Leads were connected to the corresponding CRT-P (D) device. In patients with chronic atrial fibrillation (AF), only RV and LV leads were implanted and a CRT generator was used, plugging the atrial port and programming the generator to a ventricular-triggered mode. All procedures were performed under local anaesthesia.

2.2 Clinical and ECG assessment and optimization

Patients were followed up in a dedicated device therapy clinic. Data including demographics, echocardiographic parameters, and medication at initial evaluation were retrospectively obtained from the electronic medical record. Long-term follow-up after device implantation was performed via

chart review, device interrogation or telephone interview. Echocardiographic parameters including left atrial diameter (LAD), left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) were measured. LVEF was calculated using the modified biplane Simpson's rule from apical imaging planes.

For optimization, patients in sinus rhythm underwent transmitral Doppler-directed optimization of atrioventricular delay using an iterative technique prior to discharge and at every scheduled visit thereafter.^[9] V-V delay ranged from 0 to 40 ms, according to the standard of the shortest biventricular paced QRS duration.

2.3 Clinical response and endpoints

Response to CRT was defined as reduction in LVESV $\geq 15\%$ at 6-month follow-up.^[10] Patients who died or underwent heart transplantation within six months were regarded as non-responders. The primary endpoint was total mortality. Secondary endpoints included: cardiovascular mortality, which included transplantation or implantation of a left ventricular assist device; the composite endpoints of total mortality or heart failure (HF) hospitalization. Events were collected and adjudicated by investigators who were blinded to other study data.

2.4 Statistical analysis

Continuous variables are expressed as mean \pm SD. The Shapiro-Wilk test was used to assess normality. Comparisons between normally distributed variables were made using ANOVA, with Scheffe's F procedure for multiple comparisons. Chi-squared tests and Scheffe's post-hoc test were used to analyze categorical variables. Outcomes according to etiology were depicted using Kaplan-Meier curves; the log-rank test was used to compare survival curves. Cox proportional hazard analysis was performed to evaluate each endpoint related risk. Variables reaching a $P < 0.10$ on univariable analyses were entered in multivariable models. Statistical analysis was performed using SPSS version 22.0 (SPSS Inc., Chicago, Illinois). A two-tailed $P < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics

As shown in Table 1, there was a similar proportion of men in the DHCM and ICM groups, but compared with the ICM group, the IDCM group had a lower proportion. Compared to patients with ICM, patients with DHCM and IDCM were younger. The prevalence of left bundle branch

Table 1. Demographics, baseline clinical parameters, and pharmacological treatment of the three groups of patients.

| Parameters | DHCM (n = 16) | ICM (n = 65) | IDCM (n = 231) |
|----------------------------|---------------|---------------|----------------|
| Demographics | | | |
| Male | 12 (75%) | 60 (92.3%) | 143 (61.9%)** |
| Age, yrs | 53.3 ± 13.5 | 64.3 ± 9.8* | 57.2 ± 10.4** |
| QRS duration, ms | 158.7 ± 32.2 | 159.8 ± 20.2 | 161.3 ± 18.0 |
| LBBB | 8 (50.0%) | 57 (87.7%)* | 201 (87.0%)* |
| NYHA Class | | | |
| Class I | 1 (6.3%) | 0 (0) | 2 (0.9%) |
| Class II | 5 (31.3%) | 18 (27.7%) | 48 (20.8%) |
| Class III | 8 (50%) | 33 (50.8%) | 143 (61.9%) |
| Class IV | 2 (12.5%) | 14 (21.5%) | 38 (16.5%) |
| Echo variables | | | |
| LVEF, % | 33.6 ± 6.3 | 28.0 ± 6.3* | 28.8 ± 8.0* |
| LVEDV, mL | 219.1 ± 62.8 | 260.4 ± 78.5* | 268.7 ± 81.3* |
| LVESV, mL | 147.4 ± 51.2 | 189.8 ± 66.6* | 194.0 ± 70.9* |
| LAD, mm | 47.0 ± 7.4 | 43.5 ± 6.5 | 44.4 ± 7.5 |
| Device upgrades | 3 (18.8%) | 2 (3.1%) | 9 (3.9%) |
| CRT-D use | 9 (56.3%) | 45 (69.2%) | 94 (40.7%)*,** |
| Co-morbidity | | | |
| Hypertension | 4 (25%) | 36 (58.4%)* | 57 (24.7%)** |
| Diabetes mellitus | 4 (25%) | 24 (37.5%) | 44 (17.7%)** |
| Chronic AF | 8 (50%) | 8 (12.3%)* | 28 (12.1%)* |
| Medication | | | |
| Diuretics | 16 (100%) | 64 (98.5%) | 223 (96.5%) |
| ACEI or ARB | 13 (81.3%) | 52 (80%) | 174 (75.7%) |
| β-Blockers | 16 (100%) | 60 (92.3%) | 217 (93.9%) |
| Class III antiarrhythmics# | 6 (37.5%)# | 16 (24.6%)# | 49 (21.2%)# |
| Digoxin | 8 (50%) | 40 (61.5%) | 164 (71%) |
| Anticoagulants | 8 (50%) | 7 (10.8%)* | 25 (10.8%)* |

Data were presented as n (%) or mean ± SD. *P < 0.05 vs. DHCM; **P < 0.05 vs. ICM. ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; CRT-D: cardiac resynchronization therapy-defibrillator; DHCM: dilated hypertrophic cardiomyopathy; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy; LAD: left atrial diameter; LBBB: left bundle branch block; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA class: New York Heart Association functional class.

block (LBBB) and baseline LVEF are higher in the DHCM group than the other two groups, while the baseline LVEDV and LVESV are smaller. The groups were similar with respect to baseline NYHA class, QRS duration and LAD. Upgrading to CRT was undertaken in 3 (18.8%) patients in DHCM group, 2 (3.1%) patients in ICM group and 9 (3.9%) patients in IDCM groups. A device with defibrillator capability (CRT-D) was implanted in 9 (56.3%) patients with DHCM, with respect to 45 patients (69.2%) with ICM and

94 (40.7%) with IDCM. Hypertension was more prevalent in the ICM group, and the prevalence of diabetes was higher in the ICM group than the IDCM group. The prevalence of permanent AF was the highest in the DHCM group. Apart from a higher uptake of Anticoagulants in the DHCM group, uptake of other medications, such as angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, β-blockers, and aldosterone receptor antagonists, were similar across the groups.

3.2 Endpoints

After a median follow-up period of 3.82 years (interquartile range: 5.16 years), 58 (18.6%) patients died [DHCM: 5/16 (31.3%); IDCM: 35/231 (15.2%); ICM: 18/65 (27.8%)]. Cardiac mortality was as follows: DHCM: 4/16 (25.0%); IDCM: 27/231 (11.7%); and ICM: 15/65 (23.1%). A total of 12/312 (3.8%) patients died of non-cardiac causes.

As shown in Figure 1, the DHCM group had the highest total mortality, cardiovascular mortality, and total mortality or HF hospitalization. The results of multivariable analyses are shown in Table 2. Compared with DHCM, IDCM was associated with a lower total mortality (HR: 0.35, 95% CI: 0.13–0.90), cardiac mortality (HR: 0.29, 95% CI: 0.11–0.77), and total mortality or HF hospitalizations (HR: 0.34, 95% CI: 0.17–0.69), independent of gender, chronic AF, diabetes, and LAD. Compared with the DHCM group, total mortality, cardiac mortality, and total mortality or HF hospitalizations favored the ICM group but were not statistically significant (HR: 0.59, 95% CI: 0.22–1.61; HR: 0.54, 95% CI: 0.26–1.15, respectively).

3.3 Clinical and ECG variables

At 6-month follow-up, NYHA class, LVEF and LVESV were improved in all groups. There were similar improvements in NYHA class, LVEF and LVESV across the groups (Table 3). As shown in Figure 2, Response rate to CRT was lower in the DHCM group than in the other two groups although the differences didn't reach statistical significance. (DHCM: 56.3%; IDCM: 73.6%, ICM: 69.2%, P = 0.126).

As shown in Table 4, a lower proportion of LBBB, a higher proportion of chronic AF, and an increased LAD were found in non-responders than responders in patients with DHCM. Other baseline parameters are comparable between responders and non-responders.

4 Discussion

Clinical trials have shown that CRT is effective in patients with NICM. Patients with DHCM, however, have

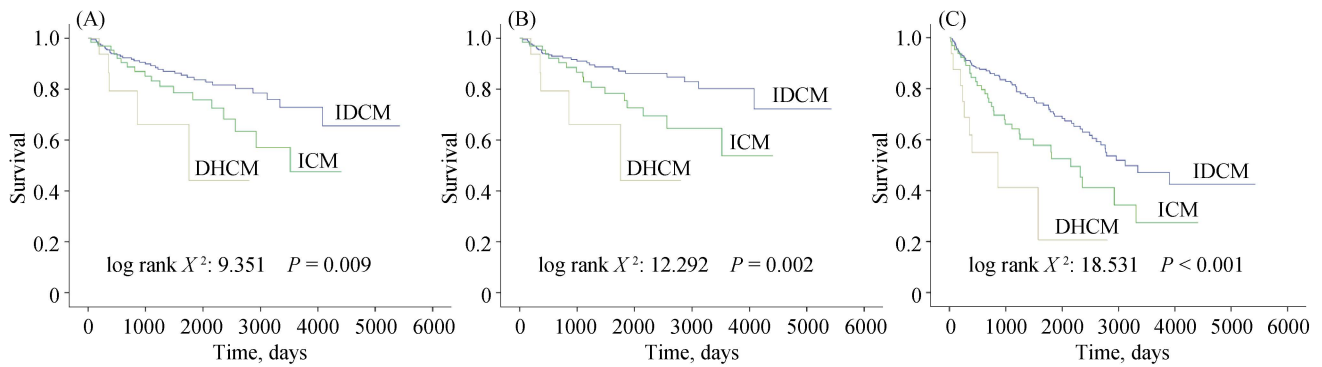


Figure 1. Mortality and morbidity after CRT. Patients were grouped according to etiology. CRT: cardiac resynchronization therapy; DHCM: dilated hypertrophic cardiomyopathy; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy.

Table 2. Univariate and multivariate analysis of baseline variables in relation to clinical outcomes.

| | Total mortality | | Cardiac mortality | | Combined endpoint | |
|----------------|------------------|---------|-------------------|---------|-------------------|---------|
| | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Univariable | | | | | | |
| Age | 1.01 (0.99–1.04) | 0.408 | 1.00 (0.97–1.02) | 0.842 | 1.00 (0.98–1.02) | 0.840 |
| Male | 1.74 (0.94–3.27) | 0.079 | 1.99 (0.99–3.98) | 0.052 | 1.70 (1.09–2.64) | 0.018 |
| Chronic AF | 1.43 (0.72–2.84) | 0.302 | 1.50 (0.73–3.08) | 0.277 | 1.58 (0.96–2.59) | 0.073 |
| LBBS | 0.61 (0.31–1.20) | 0.154 | 0.62 (0.39–1.30) | 0.211 | 0.79 (0.47–1.32) | 0.369 |
| LAD, mm | 1.05 (1.02–1.09) | 0.003 | 1.05 (1.08–1.09) | 0.004 | 1.04 (1.02–1.07) | 0.001 |
| LVEDV, mm | 1.00 (0.99–1.00) | 0.856 | 1.01 (0.99–1.02) | 0.692 | 1.00 (0.99–1.04) | 0.901 |
| LVESV, mL | 1.00 (0.99–1.00) | 0.906 | 1.00 (0.99–1.00) | 0.893 | 1.00 (0.99–1.01) | 0.196 |
| LVEF, % | 1.00 (0.96–1.03) | 0.802 | 1.00 (0.96–1.03) | 0.681 | 0.98 (0.96–1.01) | 0.153 |
| CRT-D use | 0.86 (0.50–1.46) | 0.568 | 0.92 (0.52–1.61) | 0.762 | 1.06 (0.73–1.55) | 0.749 |
| Upgrade | 1.23 (0.39–3.94) | 0.726 | 1.44 (0.45–4.63) | 0.542 | 1.37 (0.61–3.13) | 0.450 |
| DM | 1.28 (0.72–2.28) | 0.402 | 1.59 (0.88–2.88) | 0.128 | 1.66 (1.10–2.50) | 0.015 |
| Hypertension | 0.82 (0.48–1.39) | 0.463 | 0.89 (0.50–1.59) | 0.692 | 1.05 (0.70–1.57) | 0.799 |
| Anticoagulants | 1.37 (0.57–1.66) | 0.318 | 1.03 (0.58–1.82) | 0.293 | 1.31 (0.90–1.91) | 0.162 |
| DHCM | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| IDCM | 0.27 (0.11–0.74) | 0.010 | 0.24 (0.09–0.63) | 0.004 | 0.27 (0.13–0.55) | 0.001 |
| ICM | 0.50 (0.18–1.35) | 0.168 | 0.49 (0.181–1.35) | 0.167 | 0.47 (0.22–0.99) | 0.046 |
| Multivariable | | | | | | |
| Male gender | 1.17 (0.59–2.29) | 0.656 | 1.28 (0.61–2.72) | 0.514 | 1.12 (0.69–1.81) | 0.689 |
| Chronic AF | – | – | – | – | 1.38 (0.81–2.35) | 0.233 |
| LAD, mm | 1.05 (1.01–1.08) | 0.005 | 1.05 (1.01–1.09) | 0.008 | 1.03 (1.01–1.06) | 0.001 |
| DM | – | – | – | – | 0.70 (0.46–1.06) | 0.093 |
| DHCM | 1.00 (reference) | | 1.00 (reference) | | 1.00 (reference) | |
| IDCM | 0.35 (0.13–0.90) | 0.029 | 0.29 (0.11–0.77) | 0.013 | 0.34 (0.17–0.69) | 0.003 |
| ICM | 0.59 (0.22–1.61) | 0.304 | 0.59 (0.21–1.63) | 0.308 | 0.54 (0.26–1.15) | 0.111 |

Only variables with $P < 0.10$ on univariable analyses were included in multivariable models. AF: atrial fibrillation; CRT-D: cardiac resynchronization therapy-defibrillator; DHCM: dilated hypertrophic cardiomyopathy; DM: diabetes mellitus; HTN: hypertension; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy; LAD: left atrial diameter; LBBS: left bundle branch block; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; OR: odds ratio.

either been excluded or under-represented in such trials.^[6] Some case series reported that NYHA class and LVEF were improved in DHCM patients with wide QRS prolongation and LV dyssynchrony after receiving CRT,^[11–14] however,

the effects of CRT on clinical outcomes in DHCM patients were not addressed. To our knowledge, this is the first study to specifically explore the clinical outcome of patients with DHCM receiving CRT.

Table 3. Changes of clinical and ECG parameters from baseline to 6-month follow-up.

| Variable | DHCM | ICM | IDCM | <i>P</i> -value [#] |
|------------------|--------------|--------------|--------------|------------------------------|
| NYHA class | | | | |
| Baseline | 2.7 ± 0.9 | 2.9 ± 0.7 | 2.9 ± 0.6 | - |
| Follow-up | 2.4 ± 0.9 | 2.4 ± 0.7 | 2.5 ± 0.7 | - |
| Change | -0.3 ± 0.5 | -0.5 ± 0.8 | -0.5 ± 0.7 | 0.573 |
| <i>P</i> -value* | 0.020 | < 0.001 | < 0.001 | |
| LVEF, % | | | | |
| Baseline | 33.6 ± 6.3 | 28.1 ± 6.4 | 28.9 ± 8.3 | - |
| Follow-up | 40.0 ± 9.8 | 38.3 ± 9.9 | 37.9 ± 11.6 | - |
| Change | 6.4 ± 8.7 | 10.2 ± 9.4 | 9.1 ± 10.5 | 0.409 |
| <i>P</i> -value* | 0.01 | < 0.001 | < 0.001 | |
| LVESV, mL | | | | |
| Baseline | 147.4 ± 51.2 | 189.8 ± 66.6 | 194.0 ± 70.9 | - |
| Follow-up | 129.4 ± 44.6 | 147.6 ± 68.8 | 146.8 ± 74.9 | - |
| Change | 18.0 ± 32.1 | 42.2 ± 62.7 | 47.2 ± 59.5 | 0.271 |
| <i>P</i> -value* | 0.041 | < 0.001 | < 0.001 | |

Data were presented as mean ± SD **P*-value for variables between baseline and follow-up; [#]*P*-value for variables changes between different groups. DHCM: dilated hypertrophic cardiomyopathy; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA class: New York Heart Association functional class.

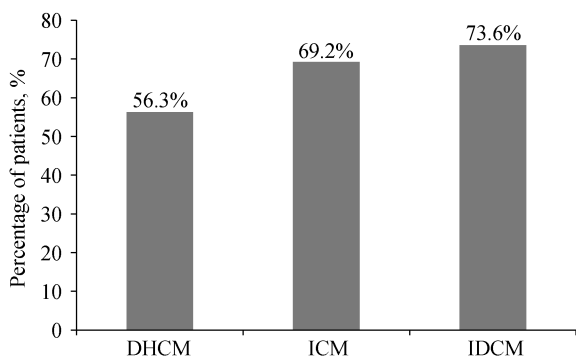


Figure 2. Responses to CRT. Patients were grouped according to etiology, namely DHCM, IDCM, or ICM. Response to CRT was defined as reduction in LVESV > 15% at 6-month follow-up. CRT: cardiac resynchronization therapy; DHCM: dilated hypertrophic cardiomyopathy; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy; LVESV: left ventricular end-systolic volume.

The clinical features of DHCM in our study were similar to those of the previous studies.^[5,15] Results of echocardiography showed that LVEDV and LVESV were smaller and EF was higher in patients with DHCM than in patients with ICM and IDCM. According to our findings, chronic AF is much more common in patients with DHCM receiving CRT than the other two groups of underlying heart

Table 4. Comparison between responders and nonresponders in patients with DHCM.

| | Responders (n = 9) | Nonresponders (n = 7) | <i>P</i> -value |
|----------------------|-----------------------|--------------------------|-----------------|
| Age, yrs | 50.9 ± 16.6 | 56.3 ± 8.0 | 0.445 |
| Male | 7 (77.8%) | 5 (71.4%) | 0.608 |
| NYHA class III/IV | 7 (77.8%) | 3 (42.9%) | 0.182 |
| Atrial fibrillation | 2 (22.2%) | 6 (85.7%) | 0.020 |
| QRS duration, ms | 171.9 ± 33.7 | 141.7 ± 22.0 | 0.050 |
| Baseline LVEF, % | 31.7 ± 6.4 | 36.1 ± 5.7 | 0.180 |
| Baseline LVESV, mL | 160.5 ± 48.7 | 137.8 ± 51.8 | 0.383 |
| Baseline LA, mm | 43.7 ± 6.4 | 51.3 ± 6.7 | 0.036 |
| Max LV thickness, mm | 13.0 ± 4.2 | 17.7 ± 7.5 | 0.127 |
| LBBB | 7 (77.8%) | 1 (16.7%) | 0.020 |
| Device upgrade | 1 (11.1%) | 2 (28.5%) | 0.400 |
| CRT-D device | 5 (55.6%) | | 0.329 |
| DM | 2 (22.2%) | 2 (28.6%) | 0.608 |
| Hypertension | 2 (22.2%) | 2 (28.6%) | 0.608 |

Data were presented as *n* (%) or mean ± SD. CRT-D: cardiac resynchronization therapy-defibrillator; DHCM: dilated hypertrophic cardiomyopathy; DM: diabetes mellitus; ICM: ischemic cardiomyopathy; IDCM: idiopathic dilated cardiomyopathy; LA: left atrium; LBBB: left bundle branch block; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; NYHA class: New York Heart Association functional class.

disease, being present in half of the cases, in consistent with the results from a previous study.^[16] The use of medications was similar between different groups. An important difference was higher use of warfarin in the DHCM group, which was in parallel to high prevalence of chronic AF. Another difference was a lower prevalence of LBBB in the DHCM group.

It is well recognized that the clinical outcome of CRT is worse in patients with ICM than those with NICM.^[17] In this study, we have identified a subgroup of NICM which appears to behave differently after CRT, namely DHCM. In this study, we found that the long-term outcome of DHCM patients receiving CRT is worse than IDCM patients, with a trend towards a worse outcome in comparison with ICM patients. We think that the poor outcome of patients with DHCM receiving CRT was mainly associated with the clinical and pathologic characteristics of DHCM. As we know, DHCM is the end stage of HCM that lead to pump failure. Although HCM is generally associated with mild disability and normal life expectancy, patients with DHCM had an extremely poor prognosis with an overall survival rate of 46% at 5 years from diagnosis of the dilated phase.^[18] Previous studies showed that the prognosis of patients with DHCM was significantly worse than that of the patients

with IDCM despite similar or even more intensive treatment for HF.^[15,19] In our study, a lower baseline LVEF and presence of ventricular dyssynchrony based on the current guideline for CRT may further contribute to worse prognosis of the patients with DHCM.

Previous studies have demonstrated that the response to CRT is different in patients with IDCM and ICM,^[17,20] but no data are available on the response to CRT in patients with DHCM. In our population sample, more than half of the patients with DHCM were classified as responders and their clinical and echocardiographic parameters were significantly improved at 6 months. However, we found that the response rate to CRT was lower in the DHCM group than the other two groups although the differences didn't reach statistical significance. After dividing the patients with DHCM into two groups based on their response status to CRT, we found that presence of LBBB, absence of chronic AF, and a smaller LAD are associated with favorable response to CRT. These findings have important implications for selecting eligible DHCM patients for CRT and predicting their clinical outcomes. Moreover, considering a lower proportion of baseline LBBB and a higher proportion of chronic AF in DHCM patients, it's not surprising that the response rate to CRT is lower in DHCM group than the other groups.

4.1 Clinical implications

Our study demonstrated that long-term outcomes were worse in DHCM patients and the response rate to CRT at six months in patients with DHCM appears to be lower than that in IDCM or ICM patients. We suspected that our findings of a poor outcome and low response rate from CRT in patients with DHCM may partly relate to the delay between the diagnosis of DHCM and delivery of CRT (5.9 years). Because HCM is a hyperdynamic disease, the bar used to define LV dysfunction should be set higher than in other cardiovascular conditions. LVEF \leq 35% as an indication of CRT implantation may not be suitable for DHCM patients, because by that time, their LV function were severely impaired and a high proportion of patients were suffered from chronic AF and enlarged LA.^[18] As a result, the window of opportunity for decisive therapeutic options such as CRT may be missed. This raises the possibility that earlier implantation of CRT may improve outcomes in patients with DHCM.

4.2 Limitations of the study

This was a retrospective, single-center, observational study with a relatively small patient cohort, which was therefore subject to a myriad of biases, particularly selection

bias and statistical power limitations. Hence, results from the current study need to be confirmed in further large-scale clinical trials. Moreover, this is a non-controlled study, and therefore, no conclusions can be drawn as the possible benefits of CRT. Finally, atrioventricular node ablation was not performed in patients with chronic AF in this study. However, to ensure the effects of CRT, strict heart rate control with medication was performed and a percentage of biventricular pacing > 90% was achieved in all subjects during follow-up.

4.3 Conclusions

Compared with IDCM, DHCM was associated with a worse outcome after CRT, independent of known confounders. Clinical outcomes in DHCM patients were similar to or even worse than that in ICM patients. Non-LBBB, chronic AF and increased LAD are predictors of poor response to CRT in DHCM patients.

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