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Duration of reverse remodeling response to cardiac resynchronization therapy: Rates, predictors, and clinical outcomes☆

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ABSTRACT

Background: A subset of patients undergoing cardiac resynchronization therapy (CRT) for heart failure (HF) with severe left ventricular (LV) dysfunction experience only short-lived LV reverse remodeling. Little is known about the incidence and prognosis of this finding. We sought to identify predictors of a brief response and investigated the prognosis in a retrospective study.
Methods: A total of 528 patients from a Japanese multicenter database with full echocardiography datasets were enrolled. Follow-up was 3.4 ± 1.3 years. Based on relative reduction in LV end-systolic volume (LVESV) at 6 months, we categorized patients as responders (reduction in LVESV ≥15%) and non-responders (NRs; reduction in LVESV <15%). Based on reduction in LVESV at 1–2 years, responders were subdivided into long-lasting responders (reduction in LVESV ≥15%) and brief responders (reduction in LVESV <15%).
Results: Of 328 responders, 50 (15%) were brief responders. Predictors of brief response were prior ventricular tachyarrhythmia, a non-left bundle-branch block (LBBB) intrinsic QRS pattern, and prior hospitalization for HF. The risk of all-cause death in brief responders was significantly lower than that in NRs ($P = 0.034$) and tended to be higher than that in long-lasting responders ($P = 0.080$).
Conclusions: Approximately 15% of responders were brief responders. Prior ventricular tachyarrhythmia, a non-LBBB pattern, and HF hospitalization were independent predictors of a brief response. Brief response was significantly associated with decreased risk of all-cause death compared with NRs and had a tendency toward increased risk of all-cause death compared with long-lasting responders.

1. Introduction

Cardiac Resynchronization Therapy (CRT) improves clinical status and induces left ventricular (LV) reverse remodeling in heart failure (HF) patients with severe LV dysfunction [1–6]. Based on the extent of echocardiographic response to CRT, including reduction in LV end-systolic volume (LVESV) and improvement in LV ejection fraction (LVEF), patients have been divided into "responders" and "non-responders (NRs)." Approximately two-thirds of CRT recipients are responders, which is associated with decreased risk of all-cause death [7–10], hospitalization for HF [11], and ventricular tachyarrhythmia (VTA) [12,13].

In most prior studies of CRT effectiveness, the durability of the response was not examined when defining echocardiographic responders [14]. The effect has been reported to change over time after implantation [13], and LV reverse remodeling has been noted by clinicians to be temporary and reversible in some patients, but sustained over several years in other responders.

In this study, we defined "brief responders" as responders with diminishing LV reverse remodeling over 1–2 years after implantation and "long-lasting responders" as responders with durable LV reverse remodeling. We analyzed a cohort of CRT recipients to determine 1) the proportion of brief responders, 2) baseline predictors of brief response, and 3) clinical outcomes of brief response.

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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2. Methods

2.1. CUBIC registry

This study was conducted as a retrospective analysis of CUBIC (CRT Utilization By Interventional Cardiologists) registry cases. The CUBIC registry is a Japanese multicenter registry of 995 patients who underwent CRT-pacing (CRT-P) or CRT-defibrillator (CRT-D) implantation at 11 institutions. Originally, the CUBIC registry was established as part of the CUBIC trial, which investigated the difference in clinical outcomes and response to CRT between ischemic and non-ischemic cardiomyopathy. A total of 307 patients who underwent implantation between May 2008 and November 2010 were prospectively enrolled and followed for > 1.5 years, while 688 patients who underwent device implantation between April 2004 and September 2008 were retrospectively enrolled and followed for up to 5 years. The protocol was approved by the institutional review board at each participating center, and all patients gave informed consent for the use of their data.

2.2. Patients

We extracted 995 cases and looked for complete echocardiographic datasets at baseline, 6 months, and 1–2 years after implantation. The echocardiogram data were analyzed in a core laboratory. Because of incomplete data, 467 cases were excluded. The remaining 528 cases were divided into responders and non-responders (NRs) categories based on the reduction in LVESV at 6 months. Responders had a relative reduction of LVESV ≥ 15%, while NRs had a relative reduction of LVESV < 15% or an increase. Responders were further subdivided based on the reduction in LVESV at 1–2 years; brief responders had a relative reduction of LVESV < 15% or an increase, and long-lasting responders continued to have a relative reduction of LVESV ≥ 15%.

2.3. Predictors and clinical outcomes of a brief response

We identified clinical predictors associated with brief responders, comparing them with long-lasting responders. We performed survival analysis of the primary and secondary endpoints among the three subgroups. The primary endpoint was all-cause death. The secondary endpoints were death from HF, HF hospitalization, and ventricular tachyarrhythmia (VTA), including a history of sustained ventricular tachycardia and ventricular fibrillation in CRT-P patients and adequate ICD therapy in CRT-D patients. We assessed clinical outcomes in brief responders and compared it with long-lasting responders and NRs by multivariable Cox proportional hazards models adjusted with several clinical parameters.

2.4. Further classification of late responders and true non-responders

A subgroup of NRs show delayed response 1–2 years after implantation. Therefore, NRs were further subdivided based on the reduction in LVESV at 1–2 years; late responders had a relative reduction of LVESV ≥ 15%, and true non-responders continued to have a relative reduction of LVESV < 15% or an increase. We compared clinical outcomes among the four groups.

2.5. Statistical analysis

We included 38 covariates as potential predictors in the analysis of predictors of brief response. In univariate analysis of covariates of interest, paired continuous variables were analyzed using Student's *t*-test, and categorical variables were analyzed using the chi-squared test comparing brief responders and long-lasting responders. Multivariate logistic regression analysis was used to determine the independent predictors of a brief response. The pool of variables considered were those found to be significant at a pre-specified $P < 0.10$ in a univariate analysis.

For survival analysis, primary and secondary endpoints were identified using the Kaplan-Meier method with a log-rank test. In univariate analysis of covariates among the groups, continuous variables were analyzed using one-way analysis of variance (ANOVA) with Tukey's post-hoc analysis, and categorical variables were analyzed using the chi-squared test. Adjusted multivariable Cox proportional hazards regression analyses were performed to assess for correlation between brief response and each outcome. The pool of variables considered were those found to be significant at a pre-specified $P < 0.10$ in a univariate analysis. All data are expressed as the mean ± standard deviation. All *P* values reported are 2-sided with a pre-specified significance of $P < 0.05$. Analyses were performed with MedCalc software version 15.8 (MedCalc Software bvba, Acacialaan 22, 8400 Ostend, Belgium).

3. Results

3.1. Patients

The study included patients receiving CRT-D devices ($n = 363$, 69%) and CRT-P devices ($n = 165$, 31%). Mean age was 68.6 ± 11.3 and 68% were male. Twenty-seven percent of patients had ischemic heart disease as the primary etiology of HF and 74% were New York Heart Association (NYHA) functional class III or IV. At baseline, mean LVEF was 28.0 ± 9.2% and LVESV was 133.5 ± 61.2 mL. QRS duration was 153.8 ± 32.7 ms and 41% of patients had an intrinsic left bundle-branch block (LBBB) QRS pattern. In Fig. 1, a total of 328 patients (62%) were classified as responders and 200 (38%) patients as NRs. Of the 328 responders, 50 (15%) were brief responders and 278 (85%) were long-lasting responders. Supplementary File 1 shows time course of echocardiographic parameters of each subgroup. Brief responders showed short-lived LV reverse remodeling (at baseline, 6 months and 1–2 years follow-up, LVESV; 136.5 ± 60.1 mL, 95.9 ± 48.1 mL and 135.4 ± 62.9 mL, respectively, LVEF; 27.6 ± 9.8%, 36.2 ± 13.4% and 30.1 ± 8.5%, respectively). Long-lasting responders showed durable LV reverse remodeling (LVESV; 132.5 ± 56.5 mL, 77.6 ±

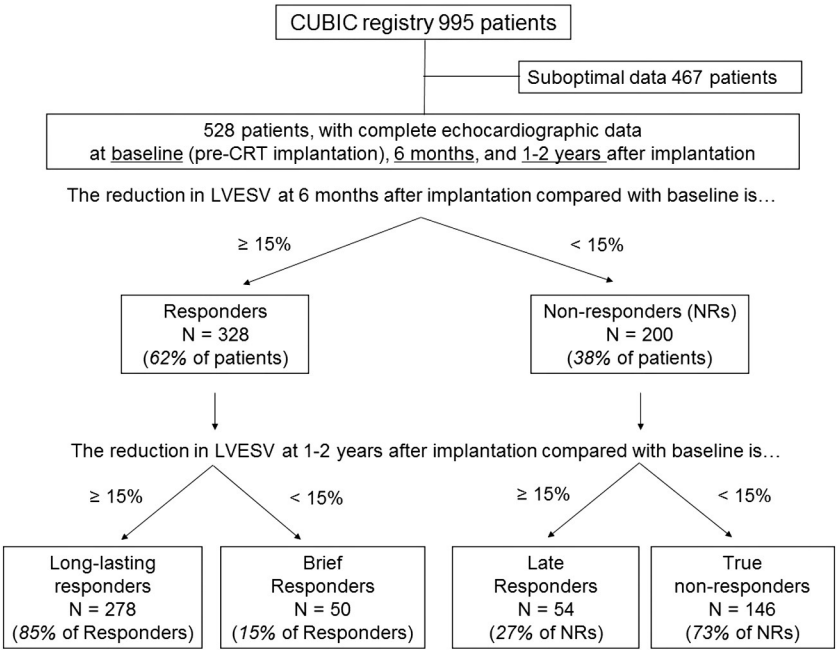

Fig. 1. Flow diagram demonstrating division of study population into responders and non-responders, with subsequent subgrouping of responders into long-lasting responders and brief responders and subsequent subgrouping of non-responders into late responders and true non-responders.

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