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Original article

Optimal cut-off value of reverse remodeling to predict long-term outcome after cardiac resynchronization therapy in patients with ischemic cardiomyopathy

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ABSTRACT

Background: Whether the optimal cut-off value of left ventricular (LV) reverse remodeling is different in patients with ischemic cardiomyopathy (ICM) vs. non-ischemic cardiomyopathy (NICM) is unclear. This study aimed to clarify this value in patients with ICM and NICM.

Methods and results: LV reverse remodeling was defined as a reduction in LV end-systolic volume (LVESV) at 6 months after cardiac resynchronization therapy (CRT). The clinical endpoint was the combination of cardiac death and first hospitalization for worsening heart failure. Ninety-one of 372 patients had ICM. Event-free survival rates did not differ between ICM and NICM groups (66.8% vs. 78.9%; $p = 0.12$). Receiver operating characteristics analysis revealed a 9% reduction in ESV as the optimal cut-off value to predict the composite endpoint in patients with ICM and a 15% reduction in patients with NICM. Multivariate analysis revealed that reductions in ESV of $\geq$15% and $\geq$9% were independent predictors of the composite endpoint, as were left bundle branch block (LBBB) and B-type natriuretic peptide (BNP) at 6 months after CRT. In combination with LBBB and BNP, reduction in ESV $\geq$9% had a higher, but not significant, *C*-statistics value than ESV $\geq$15% (0.854, 95% CI 0.729–0.940 vs. 0.801, 95% CI 0.702–0.908, $p = 0.07$).

Conclusion: The optimal cut-off value of a reduction in LVESV was lower in patients with ICM than in patients with NICM.

Introduction

Cardiac resynchronization therapy (CRT) improves mortality and symptoms of heart failure (HF) by causing volumetric and functional changes in the left ventricle in patients with HF refractory to optimal medical therapy [1]. A reduction in left ventricular (LV) end-systolic volume (ESV) after initiation of CRT is recognized as LV reverse remodeling. However, there is a wide range of variation in response to CRT, which may be a result not only of the degree of electrical dyssynchrony but also the location and characteristics of the LV pacing site. The magnitude of LV reverse remodeling relates to prognosis [2,3], and is widely used as a surrogate of response to CRT. Several studies have reported that patients with ischemic cardiomyopathy (ICM) have a lower degree of reverse remodeling than patients with non-ischemic cardiomyopathy (NICM) [4,5]. Despite these differences, the degrees of reduction in the risk of mortality and the rate of cardiovascular hospitalization from CRT were similar between patients with ICM and NICM [6]. Therefore, we hypothesized that the optimal cut-off value of LV reverse remodeling to predict clinical outcome after CRT might be different between ICM and NICM. The aim of this study was to

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clarify the optimal cut-off value of LV reverse remodeling in patients with ICM and NICM.

Methods

Study populations

This study is a retrospective data analysis combining two separate multicenter prospective cohort studies of patients undergoing CRT in Japan [the Japan Cardiac Resynchronization Therapy Registry Trial (J-CRT study) and the Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy study (START study)]. The design, protocol, and primary results of the J-CRT and START studies were reported previously [7,8]. Inclusion criteria for the two studies were nearly identical: patients with congestive HF refractory to optimal medical therapy, QRS duration of 120 ms or more, and LV ejection fraction (EF) of 35% or less. Patients classified as New York Heart Association (NYHA) class III or IV were eligible in the J-CRT study, whereas patients classified as NYHA class II, III, or IV were included in the START study. Patients were excluded if they were scheduled for catheter intervention or cardiac surgery or expected to be lost to follow-up during the first year after CRT or to die within 1 year because of non-cardiac disease. Patients underwent clinical evaluation and echocardiography before and at 1 week and 6 months after CRT. Clinical outcomes were assessed after 6 months (180 days) after initiation of CRT. At that time, 24 of the 225 patients initially enrolled in the J-CRT study were excluded because of loss to follow-up ($n = 9$), incomplete data ($n = 2$), death from any cause within 6 months ($n = 12$), or discontinuation of CRT immediately after implantation ($n = 1$). In the START study, 9 of the initially enrolled 180 patients were excluded due to incomplete data ($n = 1$) or death from any cause ($n = 8$). Finally, a total of 372 patients (201 in the J-CRT study and 171 in the START study) were enrolled in the present study. The clinical characteristics of the patients in the J-CRT and START studies are summarized in Table 1. For secondary data use, we explained the point of the present study to the steering committee of each study and got approval from them. The present study was approved by the local research ethics committee of the University of Tsukuba Hospital. All patients gave their written informed consent in each study and were informed of the point of the present study by publication on the web site.

Reverse remodeling and clinical endpoints

Serial echocardiographic studies were performed before and at 6 months after CRT to evaluate patient response to CRT. All tests were performed by cardiologists or well-trained sonographers in each individual center. The LV end-diastolic volume (LVEDV), LVESV, and LVEF were assessed by the biplane Simpson's equation in apical 4-chamber and 2-chamber views. LV reverse remodeling was defined as a reduction in LVESV at 6 months after CRT. The clinical endpoint was the combination of cardiac death and first hospitalization for worsening HF. Clinical endpoints occurring up to 6 months after CRT were excluded.

Statistical analysis

Results are expressed as number (%), as mean ± SD, or median and interquartile rage if variables were not normally distributed. Comparisons of data were performed using the Student *t*-test for unpaired continuous variables, the Mann–Whitney's *U* test for continuous variables which were not normally distributed, and chi-square tests for categorical variables. Kaplan–Meier curves were plotted to describe the composite endpoints of event-free survival, and the log-rank test was used to compare survival between groups. The diagnostic performance of reverse remodeling to predict composite outcome was assessed by receiver-operating characteristic (ROC) curve. The optimal cut-off values of reverse remodeling were chosen to maximize the value of (sensitivity + specificity − 1). The Cox proportional hazards model was used to estimate hazard ratios. The predicted probabilities to predict outcomes were calculated by a multiple logistic regression model. Using ROC analysis, *C*-statistics were estimated to evaluate the accuracy of the multiple logistic regression models.

A *p*-value of <0.05 was considered statistically significant. Statistical analysis was performed using commercially available software (JMP statistical software, SAS Institute, Cary, NC, USA). Comparisons of the area under the curve (AUC) were performed with Analyse-it (Analyse-it Software, Ltd., Leeds, UK).

Results

The clinical characteristics of the patients with ICM and NICM can be compared in Table 2. Patients with ICM were older than those with NICM, and male sex was more prevalent in ICM

Table 1
Baseline characteristics of J-CRT, START, and all patients.

	All ($N = 372$)	J-CRT ($N = 201$)	START ($N = 171$)	*p*-Value*
Clinical variables				
Age, years	65.6 ± 12.1	65.1 ± 11.8	66.1 ± 12.4	0.46
Male sex, no. (%)	252 (67.9)	139 (69.5)	113 (66.1)	0.48
ICM, no. (%)	91 (24.5)	58 (28.9)	33 (19.3)	0.03
NYHA class	2.9 ± 0.5	3.1 ± 0.3	2.7 ± 0.6	<0.0001
II	82 (22.1)	0 (0)	62 (36.2)	
III	262 (70.6)	181 (90.5)	101 (59.1)	
IV	27 (7.3)	19 (9.5)	8 (4.7)	
QRS duration, ms	160.1 ± 30.6	161.4 ± 30.9	158.6 ± 30.3	0.38
LBBB, no. (%)	234 (62.9)	148 (73.6)	86 (50.3)	<0.0001
BNP	411 [187–864]	481 [224–863]	343 [137–892]	0.14
Medication/device				
ACE inhibitor/ARB, no. (%)	296 (79.5)	166 (82.6)	130 (76.0)	0.12
β-Blocker, no. (%)	289 (77.7)	151 (75.1)	138 (80.7)	0.20
Loop diuretics, no. (%)	305 (81.9)	163 (81.1)	142 (83.0)	0.63
Defibrillator, no. (%)	216 (59.0)	74 (37.8)	142 (83.0)	<0.0001

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BNP, B-type natriuretic peptide; ICM, ischemic cardiomyopathy; J-CRT, Japan Cardiac Resynchronization Therapy Registry Trial; LBBB, left bundle branch block; NYHA, New York Heart Association; START, Speckle Tracking Imaging for the Assessment of Cardiac Resynchronization Therapy study.
* J-CRT vs. START.

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