Predictors and outcomes of cardiac resynchronization therapy extended to the second generator

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BACKGROUND A proportion of patients who receive cardiac resynchronization therapy with defibrillator (CRT-D) live to receive a second generator. Controversy exists on whether an implantable cardioverter-defibrillator (ICD) should be offered to patients who have normalized or near-normalized left ventricular ejection fraction (LVEF) at the time of generator replacement (GR).

OBJECTIVE The purpose of this study was to evaluate incidence of appropriate ICD therapy after CRT-D GR.

METHODS This series involved 1026 consecutive patients who underwent CRT-D implant between January 2002 and December 2012. Echocardiography was assessed before the initial device implant and before GR. ICDs were monitored at our device clinic in person or remotely, or both.

RESULTS Of the cohort, 227 patients (22.1%) underwent CRT-D GR at our institution. Approximately 48% of the patients who received new CRT-D generators were no longer meeting the guidelines indication for ICD use at the time of GR. These patients received subsequent appropriate ICD therapies at a significantly lower rate than those with LVEF <35% (12% vs 35%; $P < .001$). Of these patients, 47 (20.7%) had LVEF improvement to ≥50% at the time of GR. ICD therapy for ventricular arrhythmia in the ischemic group was 18.2%, while no patient in the nonischemic group received ICD therapy from the second generator after GR.

CONCLUSION Improvement in LVEF after CRT-D GR is associated with significantly reduced incidence of appropriate ICD therapy. Ventricular arrhythmia is less likely to develop with normalized LVEF in nonischemic cardiomyopathy.

KEYWORDS Cardiac resynchronization therapy; Defibrillator therapy; Generator replacement; Mortality; Outcome

(Heart Rhythm 2017;■:1–8)

Introduction

Cardiac resynchronization therapy (CRT) improves left ventricular (LV) function, survival, and quality of life for patients with systolic heart failure and prolonged QRS duration.[1–5] Clinical trials and practice have consistently shown favorable long-term outcomes of CRT.[6–10] As a result, some CRT recipients may live to receive a second or third generator. Patients who have improvement or normalization of LV ejection fraction (LVEF) have a reduced risk of arrhythmic sudden death, raising a question about the benefit of implantable cardioverter-defibrillator (ICD) at the time of generator replacement (GR).[11–14] Can CRT with defibrillator (CRT-D) be downgraded safely to CRT with pacemaker for patients whose LVEF has normalized? To gain this information, we proposed to study patients who had received a second CRT-D generator and subsequent ICD therapy for ventricular tachycardia (VT) or ventricular fibrillation (VF). The objectives of this study were to evaluate the incidence of appropriate ICD therapy after CRT-D GR and to identify the predictive factors for CRT-D GR.

Methods

Study patients

We conducted a single-center retrospective study of 1026 consecutive patients who received CRT-D at Mayo Clinic in Rochester, Minnesota, between January 2002 and December 2012. Patients received their initial CRT devices according to American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines.[15,16] The Mayo Clinic Institutional Review Board approved this study.

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1547-5271/$-see front matter https://doi.org/10.1016/j.hrthm.2017.09.002

Baseline evaluation

All patients had a baseline clinical evaluation before the first CRT device implant. The evaluation included assessment of New York Heart Association (NYHA) functional class, heart failure etiological factors, concomitant cardiovascular conditions, medication use, electrocardiographic QRS duration and morphological characteristics, and transthoracic echocardiography.

Patient follow-up

Clinical and echocardiographic follow-up examinations were performed within 12 months after CRT device implant. NYHA class and echocardiography were reassessed at follow-up. When a patient was considered for CRT-D GR at the end of battery life for the first generator, a repeat echocardiographic assessment was obtained within 12 months of GR.

Tachycardia detection and therapy of CRT-D devices were programmed in a standard manner for primary sudden death prevention in our institution across all manufacturers since 2010 (VT zone: 170 beats/min, monitor only; VF zone: 200 beats/min). For the VF zone, antitachycardia pacing (ATP) was programmed as an initial therapy, followed by high-energy shocks. All patients were observed with a remote monitoring system. The *primary outcome* was defined as the first appropriate ATP or shock therapy for sustained VT or VF for the first generator and after GR. Survival information was obtained from the electronic health record and the national death and location database (Accurint, LexisNexis; data obtained on November 2015).

Statistical analysis

Categorical variables were compared between patients and controls using the χ^2 test or Fisher exact test; continuous variables were compared using the 2-sample *t* test or Wilcoxon rank sum test, as appropriate. The Kaplan-Meier method was used for survival and freedom from ATP and shock therapies after GR. Cox proportional hazards models were used to assess the univariate and multivariate predictors of outcome end points. The multivariate model includes univariate significant variables ($P < .05$). All statistical tests were 2-sided, with α set at .05 for statistical significance.

Results

Baseline characteristics

The patient characteristics at the initial CRT-D implant are listed in Table 1. The mean age of the study patients was 69 years (male sex 78%). Of 1026 CRT-D recipients, 231 patients had GR. Of these, 227 (22.1%) underwent CRT-D GR and had sufficient echocardiographic data for LV function assessment within 1 year of GR. Four patients who had GR without echocardiographic data at the time of GR were not included in the analysis. The first generator's mean battery life was 4.9 ± 1.6 years. In total, 421 patients (41%) died before GR (median survival time 861 days). By comparison, 198 patients (19%) had a functioning first generator battery at the time of last follow-up. The other 176 patients (17%) did not return to our hospital for consideration of GR.

Predictors of GR

The univariate predictors of GR are summarized in Table 1. Female sex and lower LVEF appeared to be associated with GR. After a multivariate Cox regression analysis, only female sex was more likely than male sex to undergo GR (hazard ratio [HR] 1.37; 95% confidence interval [CI] 1.04–1.82; $P = .03$).

The mean battery life was 50 ± 18 months for the manufacturer Medtronic, Inc., 59 ± 19 months for Boston Scientific Corporation, and 56 ± 10 months for St. Jude

Table 1 Patient baseline characteristics

Variable	Patients with no GR (n = 799)	Patients with GR (n = 227)	HR	95% CI	*P*
Age (y)	69.4 ± 12.0	66.6 ± 11.4	1.00	0.99–1.01	.53
Female sex	190 (20.7)	72 (31.2)	1.37	1.04–1.82	.03
DCM	398 (45.6)	117 (50.6)	1.14	0.88–1.48	.32
LVEF (%)	25.6 ± 8.9	23.6 ± 6.8	0.79	0.67–0.93	.01
Hypertension	336 (36.7)	81 (35.1)	0.86	0.65–1.12	.26
Atrial fibrillation	471 (51.4)	107 (46.3)	0.81	0.63–1.06	.12
Diabetes mellitus	287 (31.3)	66 (28.6)	1.18	0.89–1.57	.26
Stroke	37 (31.3)	10 (4.3)	1.18	0.63–2.23	.60
NYHA functional class III/IV	503 (71.3)	147 (70.0)	1.19	0.89–1.60	.24
Statin	353 (63.6)	44 (54.3)	0.86	0.56–1.34	.50
Digoxin	409 (45.8)	122 (56.0)	1.49	1.14–1.95	.01
β-Blocker	791 (88.5)	194 (88.6)	0.82	0.54–1.24	.34
ACEI or ARB	692 (77.6)	192 (87.7)	1.45	0.97–2.17	.07
Aldactone	270 (30.3)	59 (27.2)	1.09	0.81–1.47	.58
LBBB	409 (46.7)	111 (49.1)	1.08	0.83–1.41	.55
RBBB	65 (7.4)	12 (5.3)	0.75	0.42–1.35	.337

Values are presented as mean ± SD or as n (%) unless indicated otherwise.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; DCM = nonischemic (dilated) cardiomyopathy; GR = generator replacement; HR = hazard ratio; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; RBBB = right bundle branch block.