Brief Report

Should Cardiac Resynchronization Therapy Be a Rescue Therapy for Inotrope-Dependent Patients With Advanced Heart Failure?

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ABSTRACT

Background: Although the ''off-label usage'' of cardiac resynchronization therapy with defibrillator (CRT-D) has spread recently in advanced heart failure (HF) patients in the real-world practice, its clinical effect remained uncertain.

Methods and Results: A total of 84 in-hospital <65-year old patients with advanced HF undergoing CRT-D were enrolled. Seventeen patients (20%) had been dependent on inotropes at the time of CRT-D implantation, and 17 suffered cardiac death within a year. Both inotrope dependence and elevated plasma levels of B-type natriuretic peptide (BNP) (>690 pg/mL) at the time of CRT-D implantation were independent predictors of cardiac death within a year by Cox regression analyses ($P < 0.05$ for both). These 2 parameters could significantly stratify 1-year ventricular assist device (VAD)-free survival: inotrope-free low (1) or high BNP (2), or inotrope-dependent low (3) or high BNP groups (4) (98, 77, 57, and 17%, respectively, $P < 0.001$). In contrast, there were no significant differences in actual 1-year survival among the four groups.

Conclusion: Patients dependent on inotropes sometimes receive CRT-D therapy as the last treatment resort in clinical practice, but LVAD implantation should be considered instead of CRT-D in advanced HF patients because of their poor prognosis with CRT-D therapy. (*J Cardiac Fail 2015;21:535–538*)

Key Words: INTERMACS, ventricular assist device, catecholamine, reverse remodeling.

Clinical trials have demonstrated that cardiac resynchronization therapy–defibrillator (CRT-D) use improves functional status, morbidity, and survival in select patients with heart failure (HF).[1] In recent clinical practice, CRT-Ds have been used in advanced HF patients, such as those dependent on inotrope infusion, despite lack of established indications for its use in current treatment guidelines. Treatment with a left ventricular assist device (LVAD) has been increasingly used as definitive cardiac replacement therapy in patients with advanced HF,[2] and some patients receive LVAD therapy soon after implantation of a CRT-D owing to deteriorating hemodynamics.[3] However, it is unknown what factors are associated with such inefficient utilization of CRT-D.

Methods

We enrolled 84 patients aged <65 years who were hospitalized with advanced HF (New York Heart Association [NYHA] functional class III or IV despite adequate medical therapy) and received a CRT-D device from 2007 to 2014. The indication for CRT-D implantation was NYHA functional class III or IV HF with left ventricular (LV) diastolic dimension >55 mm, LV ejection fraction <35%, QRS interval >120 ms, or mechanical dyssynchrony with narrow a QRS. No participant had a contraindication to LVAD therapy or heart transplantation at the time of CRT-D implantation. The protocol was approved by the Institutional

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Table 1. Cox Regression Analyses for Cardiac Death Within 1 Year After the Implantation of CRT-D Among Baseline Variables

	Cardiac Death (n = 17)	No Cardiac Death (n = 67)	Univariate Analyses		Multivariate Analyses	
			P Value	HR (95% CI)	*P* Value	HR (95% CI)
Demographic variables						
Male, n (%)	14 (82)	54 (81)	.809	1.166 (0.335−4.057)		
Age, y	46 ± 11	50 ± 13	.166	0.976 (0.942−1.010)		
BMI	21.1 ± 3.8	23.1 ± 4.6	.171	0.918 (0.812−1.038)		
SBP, mm Hg	86 ± 12	100 ± 12	.001*	0.917 (0.878−0.958)		
SBP <90 mm Hg, n (%)	13 (76)	16 (24)	.001*	7.721 (2.513−23.72)	.565	0.572 (0.085−3.835)
Ischemic etiology, n (%)	4 (24)	6 (9)	.093	2.617 (0.853−8.031)		
Inotropes infusion, n (%)	13 (76)	4 (6)	<.001*	20.77 (6.687−64.51)	.002*	17.72 (2.794−112.3)
NYHA III, n (%)	1 (6)	54 (81)	<.001*	38.61 (5.125−290.9)		
NYHA IV, n (%)	16 (94)	12 (18)	-	-		
Laboratory variables						
Hemoglobin, mg/dL	12.4 ± 1.6	13.3 ± 1.8	.110	0.796 (0.602−1.053)		
Serum albumin, mg/dL	3.8 ± 0.6	4.0 ± 0.5	.158	0.502 (0.193−1.306)		
Serum sodium, mEq/L	135 ± 4	137 ± 3	.062	0.869 (0.776−1.010)		
Serum total bilirubin, mg/dL	1.3 ± 0.6	1.0 ± 0.6	.152	1.569 (0.847−2.097)		
Serum creatinine, mg/dL	0.9 ± 0.2	1.1 ± 0.8	.170	0.231 (0.029−1.867)		
Plasma BNP, pg/mL	920 ± 408	474 ± 318	<.001*	1.003 (1.001−1.004)		
Plasma BNP >690 pg/mL, n (%)	12 (71)	14 (21)	.002*	6.046 (1.947−18.77)	.034*	3.843 (1.111−13.30)
Echocardiographic variables						
LVDD, mm	71 ± 13	70 ± 13	.850	1.004 (0.967−1.042)		
LVEF, %	23 ± 8	26 ± 10	.352	0.974 (0.921−1.030)		
LAD, mm	47 ± 9	49 ± 9	.847	0.994 (0.936−1.056)		
AR, grade	0.3 ± 0.6	0.5 ± 0.8	.372	0.701 (0.321−1.530)		
MR, grade	2.3 ± 1.0	1.9 ± 0.9	.167	1.465 (0.852−2.517)		
TR, grade	1.8 ± 1.0	1.6 ± 0.9	.420	1.233 (0.742−2.048)		
Electrocardiographic variables						
HR, beats/min	80 ± 13	72 ± 14	0.680	1.031 (0.999−1.063)		
QRS duration, ms	127 ± 30	147 ± 36	0.047*	0.983 (0.967−1.000)		
QRS duration <135 ms, n (%)	10 (83)	24 (36)	.048*	2.100 (1.763−5.778)	.672	1.256 (0.436−3.618)
CRBBB, n (%)	0 (0)	9 (13)	.288	0.039 (0.000−15.59)		
CLBBB, n (%)	5 (42)	17 (25)	.810	1.138 (0.395−3.277)		
Previous pacing, n (%)	6 (35)	14 (21)	.348	1.610 (0.595−4.354)		
AF, n (%)	0 (0)	10 (15)	.295	0.040 (0.000−16.68)		

BMI, body mass index; SBP, systolic blood pressure; NYHA, New York Heart Association functional class; BNP, B-type natriuretic peptide; LVDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; HR, heart rate; CRBBB, complete right bundle branch block; CLBBB, complete left bundle branch block; AF, atrial fibrillation.
*$P < .05$ by Cox regression analyses.

Review Board of the University of Tokyo. Written informed consent was obtained from each patient. Baseline variables were obtained immediately before CRT-D implantation. The primary end point was cardiac death including all-cause mortality and early cardiac death, which was defined as LVAD implantation within 1 year of CRT-D implantation. Data were analyzed with the use of SPSS Statistics 22 (SPSS, Chicago, Illinois). All statistical tests were 2 tailed, and statistical significance was defined as $P < .05$.

Results

In all, 84 patients were enrolled (68 men, 28 NYHA functional class IV). Of these, 17 patients (20%) were dependent on inotropes before CRT-D implantation.

Cardiac death occurred in 17 patients during the 1st year after CRT-D implantation. Using the results of univariate analyses, multicollinearity, and receiver operating characteristic analyses, we performed multivariate Cox regression analysis, which demonstrated that inotrope dependence (hazard ratio 17.72) and B-type natriuretic peptide (BNP) level >690 pg/mL (hazard ratio 3.843) were independent predictors of early cardiac death among all baseline variables ($P < .05$ for both) (Table 1).

Using the 2 independent predictors, 1-year LVAD-free survival was stratified into 4 risk groups: (1) inotrope free, low BNP level; (2) inotrope free, high BNP level; (3) inotrope dependent, low BNP level; and (4) inotrope dependent, high BNP level (98%, 77%, 57%, and 17%, respectively; $P < .001$) (Fig. 1A). No significant differences in 1-year actual survival among the 4 groups were found (Fig. 1B).

Discussion

Although infrequently reported, ''off-label use'' of CRT-D therapy has increased in clinical practice, especially in patients with advanced HF.[4] CRT-D therapy is sometimes used as the last resort for treatment in patients who are refractory to optimal medical therapy, despite the lack of guideline-recommended indication.[1,3] In the present study, 20% of patients were dependent on inotropes and 24% had QRS duration <120 ms at the time of CRT-D implantation.