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Comparison of left ventricular reverse remodeling induced by cardiac contractility modulation and cardiac resynchronization therapy in heart failure patients with different QRS durations

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ABSTRACT

Background: Cardiac contractility modulation (CCM) is a new device-based therapy for advanced systolic heart failure with normal QRS duration and therefore not suitable for cardiac resynchronization therapy (CRT). Left ventricular (LV) reverse remodeling was reported in patients treated with CCM or CRT, however, the extent of response was not compared.
Methods: This observational study consisted of three groups of patients with symptomatic heart failure and LV ejection fraction <35% despite optimal medical therapy. Group 1 included those received CCM with a QRS duration <120 ms ($n=33$), Group 2 included those received CRT with a QRS duration of 120–150 ms ($n=43$), and Group 3 included those received CRT with a QRS duration >150 ms ($n=56$). LV end-systolic volume (LVESV) was measured at baseline and 3 months later.
Results: Age, gender, etiology of heart failure and baseline ejection fraction were comparable. A significant LV reverse remodeling was observed in each group. The degree of LVESV reduction was similar between Group 1 and Group 2 (-11.3 ± 11.8 vs. $-13.6\pm18.3\%$, $p=0.833$), however, it was greater in Group 3 ($-25.0\pm18.0\%$, both $p<0.01$). By using the reduction ≥15%, the responder rate was not different between Group 1 (39%) and Group 2 (42%), but significantly higher in Group 3 (68%) ($\chi^2=9.514$, $p=0.009$).
Conclusion: CCM exhibited a similar LV reverse remodeling response to CRT for patients with a mildly prolonged QRS, though the effect was less strong when compared to CRT for patients with a very wide QRS.

1. Introduction

Cardiac contractility modulation (CCM) is a new device therapy for advanced heart failure (HF) due to systolic dysfunction which is under continuous investigation in recent years. It works by applying a relatively high voltage electrical signal to the myocardium during the absolute refractory period of the contractile cycle. In contrast to the impulse in the pacing device therapies such as cardiac resynchronization therapy (CRT) [1], the signal does not initiate a new contraction or modify activation sequence, but exerts inotropic enhancement in the failing myocardium by stimulating an increase in the systolic level of intracellular calcium [2-5]. The safety and efficacy of CCM therapy were observed in recent clinical trials which showed improvement of symptoms, exercise tolerance and quality of life in HF patients, but not an increase in all-cause mortality or hospitalization [6-9]. In addition, left ventricular (LV) reverse remodeling after CCM was also demonstrated in both animal and human studies, though clinical data are relatively limited [5,6,10].

LV reverse remodeling has been incorporated as one of the major assessment for favorable responses of CRT in a number of clinical trials, and is less subjected to placebo effect [11]. It is usually assessed by noninvasive imaging tools such as echocardiography for the extent of reduction in LV end-systolic volume (LVESV) with gain in ejection fraction compared with baseline. Significant reverse remodeling was not only related to improvement in clinical status, but also associated with a better long-term prognosis after CRT [12-14]. Therefore, this study was aimed to compare the degree of LV reverse remodeling response induced by CCM versus CRT, the two device therapies for refractory HF.

2. Methods

2.1. Patients

From January, 2005 to December, 2008, this study enrolled a total of 132 patients with advanced HF who had New York Heart Association (NYHA) class III or IV symptoms with LV ejection fraction <35% despite optimal medical therapy. They were categorized

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into the following 3 groups: Group 1, the patients who received CCM treatment (Optimizer III System, IMPULSE Dynamics, Inc., Orangeburg, NY) with a QRS duration on surface ECG at baseline of <120 ms, not eligible for CRT ($n=33$); Group 2, the patients who received CRT with a QRS duration of 120–150 ms ($n=43$); Group 3, the patients who received CRT with a QRS duration of >150 ms ($n=56$). The 2 CRT groups served as the control groups to the CCM group where a newer and different device therapy was attempted. The inclusion and exclusion criteria for CRT were compatible with current guidelines [15].

CCM was initiated in patients who had advanced congestive HF with a narrow QRS complex and therefore were not candidates for CRT based on current guidelines [15]. Other major exclusion criteria of CCM therapy consisted of the following conditions: qualified for heart transplant, frequent premature ventricular contraction, permanent or persistent atrial fibrillation, aortic or tricuspid mechanical prosthetic valve, hospitalization for acute exacerbation of HF within 2 weeks, unstable angina within 1 month, or acute myocardial infarction within 3 months of study entry. Details of the CCM or CRT system implantation have been provided previously [7,11,16]. The CCM device system (Optimizer III System, IMPULSE Dynamics, Inc., Orangeburg, NY) consists of a CCM signal generator and three electrodes connected to it. The implant procedure itself is also similar to that of a standard dual-chamber pacemaker. One electrode is positioned in the right atrium that used only for sensing atrial activity. The other two electrodes are positioned on the right ventricular septum, near the anterior and posterior septal grooves, that used for sensing ventricular activity and delivering CCM electrical signals. In the present study, CCM was delivered intermittently (1-hour periods distributed equally over the 24 hours of 1 day).

All patients were assessed at baseline and after 3 months of device therapy by echocardiographic evaluation of reverse remodeling as well as clinical measurement of NYHA class, Minnesota Living with Heart Failure Questionnaire (MLWHFQ) quality of life score and 6-minute hall walk test (6MHW). The study protocol was approved by the Ethics Committee of the institution and the written informed consent was obtained from each patient.

2.2. Echocardiography

Standard echocardiography (Vivid 7, Vingmed-General Electric, Horten, Norway) was performed in every patient by doctors who were blinded to the clinical conditions. Of note, in the CCM group, follow-up echocardiographic images were acquired during the time when no active CCM signals were delivered in order to blind the type of intervention. LV end-diastolic volume (LVEDV), LVESV and LV ejection fraction (LVEF) were measured by use of Biplane Simpson's method. The severity of mitral regurgitation (MR) was assessed by the ratio of MR jet area to left atrial area in percentage. Three consecutive cardiac cycles were stored and analyzed for a mean value. The intraobserver and interobserver variabilities for volumetric assessment in HF patients in our lab were 4% and 5%, respectively. A significant LV reverse remodeling was defined as the reduction in LVESV of ≥15%, or the absolute improvement in LVEF of ≥5% [17,18].

2.3. Statistics

Data were analyzed using dedicated software (SPSS for Windows, version 17.0.2, SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean ± standard deviation, while categorical data are summarized as frequencies and percentages. One-way ANOVA with Scheffe post-hoc test or Pearson Chi-square test was used when appropriate to compare among the 3 study groups. A p value of <0.05 was considered as statistically significant.

3. Results

3.1. Baseline characteristics of the study groups

As shown in Table 1, the CCM group is identical to the two CRT groups in terms of age, gender and etiology of HF, as well as blood pressure and heart rate at baseline (all $p>0.05$). However, the patients in Group 1 had fewer symptoms ($p=0.006$) and better scores for MLWHFQ ($p=0.034$) than those in Group 3. Clinical status of the patients was not different between Group 1 and Group 2 (all $p>0.05$). With respect to anti-HF medication, there was a trend that fewer patients in Group 1 were taking diuretics, aldactone and digoxin than in Group 3, but the differences did not reach statistical significance. The LVEDV, LVESV, LVEF and MR severity at baseline were similar when the CCM group was compared with the two CRT groups.

3.2. Reverse remodeling response of the study groups

In all the 3 treatment groups, the LVEDV and LVESV decreased while LVEF increased significantly at 3-month follow up (Fig. 1a–c). MR was significantly reduced in Group 1 (20 ± 15 vs. 15 ± 15%, $p=0.020$) and Group 3 (17 ± 19 vs. 11 ± 15%, $p=0.006$), and there was a trend of improvement in Group 2 (21 ± 26 vs. 16 ± 20%, $p=0.087$). As shown in Table 2, the degree of LV reverse remodeling was similar between Group 1 and Group 2, though it was significantly greater in Group 3 (all $p<0.05$). Based on the reduction of LVESV ≥15%, LV reverse remodeling was observed in 13 (39%) patients in Group 1, 18 (42%) patients

Table 1
Comparison of baseline characteristics among the study groups.

	Group 1 CCM and QRS <120 ms ($n=33$)	Group 2 CRT and QRS 120–150 ms ($n=43$)	Group 3 CRT and QRS >150 ms ($n=56$)	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Age, years	60 ± 11	65 ± 11	65 ± 14	0.254	0.179	0.991
Gender (male), *n* (%)	26 (78.8)	28 (65.1)	40 (71.4)	0.193	0.444	0.502
Etiology (ischemic), n (%)	17 (51.5)	22 (51.2)	25 (45.5)	0.976	0.582	0.575
Systolic BP, mm Hg	120 ± 22	127 ± 23	130 ± 26	0.477	0.203	0.876
Diastolic BP, mm Hg	75 ± 13	74 ± 11	74 ± 13	0.772	0.958	0.902
Heart rate, bpm	77 ± 15	76 ± 13	75 ± 10	0.982	0.474	0.606
NYHA class, *n* (%)						
III	33 (100)	41 (95.3)	45 (80.4)	0.502	0.006	0.029
IV	0	2 (4.7)	11 (19.6)			
Quality of life score	23 ± 19	29 ± 21	36 ± 25	0.527	0.034	0.314
6MHW distance, m	331 ± 82	329 ± 103	280 ± 94	0.992	0.060	0.065
QRS duration, ms	99 ± 14	133 ± 11	168 ± 18	<0.001	<0.001	<0.001
Medication, *n* (%)						
ACEI or ARB	27 (81.8)	39 (90.7)	49 (87.5)	0.315	0.540	0.616
β-blocker	25 (75.8)	34 (79.1)	42 (75)	0.731	0.936	0.635
Diuretics	22 (66.7)	34 (79.1)	47 (83.9)	0.224	0.059	0.534
Aldactone	4 (12.1)	9 (20.9)	16 (28.6)	0.312	0.073	0.386
Digoxin	3 (9.1)	7 (16.3)	13 (23.2)	0.499	0.094	0.394
LVEDV, cm^3	161 ± 40	187 ± 80	189 ± 69	0.249	0.168	0.989
LVESV, cm^3	117 ± 35	140 ± 68	143 ± 64	0.255	0.138	0.962
LVEF, %	27.7 ± 6.9	26.4 ± 7.2	26.1 ± 9.3	0.788	0.673	0.984
MR jet area, % of LA area	20 ± 15	21 ± 26	17 ± 19	0.992	0.779	0.660

6MHW, 6-minute hall-walk; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CCM, cardiac contractility modulation; CRT, cardiac resynchronization therapy; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NYHA, New York Heart Association.