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 observed 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±18.3%, p=0.833), however, it was greater in Group 3 (18.8±18.3%, p=0.009). 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%) (χ²=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.

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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...
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          | Group 2          | Group 3          | Group 1          | Group 2          | Group 3          |
| Name of parameter               | (n = 33)         | (n = 43)         | (n = 56)         | Group 1          | Group 2          | 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            | 0.201            | 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 (%)               | 33 (100)         | 41 (95.3)        | 45 (80.4)        | 0.502            | 0.006            | 0.029            |
| NY class                        | 0 ± 0            | 2 ± 4.7          | 11 ± 15.6        | 0.057            | 0.034            | 0.314            |
| Quality of life score           | 23 ± 19          | 29 ± 21          | 36 ± 25          | 0.992            | 0.060            | 0.065            |
| 6MHW distance, m                | 331 ± 82         | 329 ± 103        | 280 ± 94         | < 0.001          | < 0.001          | < 0.001          |
| QRS duration, ms               | 99 ± 14          | 133 ± 11         | 168 ± 18         | 0.315            | 0.540            | 0.616            |
| Medication, n (%)               | 39 (90.7)        | 49 (87.5)        | 49 (87.5)        | 0.731            | 0.936            | 0.635            |
| 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)        | 42 (75)          | 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, cm³                      | 161 ± 40         | 187 ± 80         | 189 ± 69         | 0.249            | 0.168            | 0.989            |
| LVESV, cm³                      | 117 ± 35         | 140 ± 68         | 143 ± 64         | 0.255            | 0.138            | 0.962            |
| LVVPE, %                        | 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.
in Group 2 and 38 (68%) patients in Group 3 ($\chi^2=9.514, p=0.009$) (Fig. 2). For the improvement of LVEF ≥5%, these figures were 18 (55%) in Group 1, 23 (53%) in Group 2 and 37 (66%) in Group 3 ($\chi^2=1.969, p=0.374$) (Fig. 2).

### 3.3. Clinical improvement of the study groups

At 3-month follow up, NYHA class was improved in all the 3 groups. MLWHFQ quality of life score was improved in the 2 CRT groups but not in the CCM group. 6MHW distance was increased in Group 1 and Group 2, while the improvement in Group 2 was not significant (Fig. 3a–c). When compared between the CCM group and the CRT groups, the improvement of NYHA class was identical while the difference in the increase of 6MHW distance between Group 1 and Group 3 was not statistically significant (Table 2). On the other hand, systolic blood pressure was not changed in Group 1 (120±22 vs 122±24), Group 2 (127±23 vs 126±21) and Group 3 (130±26 vs 134±27 mm Hg) (all $p>0.05$). Diastolic blood pressure remained constant before and after device therapy in the 3 groups as well (75±13 vs 75±15, 74±11 vs 72±11, 74±13 vs 75±12 mm Hg, all $p>0.05$). Heart rate was reduced in Group 3 (75±12 vs 69±12 bpm, $p=0.024$), but not changed in Group 1 (77±15 vs 74±12) and Group 2 (76±13 vs 74±14 bpm, both $p>0.05$).

### 4. Discussion

The present study showed that the efficacy of CCM therapy with respect to LV reverse remodeling was comparable to that of CRT in patients with a QRS duration between 120 and 150 ms. The improvement of NYHA class and 6MHW distance was also noted for CCM, which appeared comparable to the same CRT group. Nevertheless, patients with a QRS duration of >150 ms treated by CRT demonstrated the greatest extent of LV reverse remodeling and clinical improvement.

LV adverse remodeling occurs inevitably in HF that represents a progressive alteration in ventricular geometry and structure, usually in the form of increased LV volume and mass, more spherical LV shape and reduced LVEF. A number of studies have demonstrated the association between the extent of LV remodeling and cardiovascular prognosis, while LVESV is the single best predictor of adverse clinical outcome in patients with LV dysfunction [19]. Therefore, assessment of the improvement in LV size and cardiac function, i.e. LV reverse remodeling, has been widely accepted as one of the main measures for the effect of drug or device therapy in many clinical trials. Firstly, LV reverse remodeling is the structural premise to reveal the benefits of therapy on cardiac function and ventricular hemodynamics [20,21]. Secondly, it is an objective endpoint which can be

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**Table 2**

<table>
<thead>
<tr>
<th>Reverse Remodeling</th>
<th>Group 1 CCM &amp; QRS ≤120 ms</th>
<th>Group 2 CRT &amp; QRS 120–150 ms</th>
<th>Group 3 CRT &amp; QRS &gt;150 ms</th>
<th>Group 1 vs Group 2</th>
<th>Group 1 vs Group 3</th>
<th>Group 2 vs Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in LVEDV, %</td>
<td>-4.6±9.6</td>
<td>-7.6±13.9</td>
<td>-15.5±15.5</td>
<td>0.632</td>
<td>0.002</td>
<td>0.020</td>
</tr>
<tr>
<td>Change in LVESV, %</td>
<td>-11.3±11.8</td>
<td>-13.6±18.3</td>
<td>-25.0±18.0</td>
<td>0.833</td>
<td>0.002</td>
<td>0.005</td>
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<tr>
<td>Change in LVEF (absolute), %</td>
<td>5.3±4.6</td>
<td>5.3±7.4</td>
<td>8.7±7.4</td>
<td>1.000</td>
<td>0.087</td>
<td>0.055</td>
</tr>
<tr>
<td>Change in MR (absolute), %</td>
<td>-5±11</td>
<td>-5±18</td>
<td>-6±17</td>
<td>0.998</td>
<td>0.853</td>
<td>0.864</td>
</tr>
</tbody>
</table>

**Clinical Improvement**

<table>
<thead>
<tr>
<th>Change in NYHA class, n (%)</th>
<th>Group 1 vs Group 2</th>
<th>Group 1 vs Group 3</th>
<th>Group 2 vs Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement of 2 classes</td>
<td>0</td>
<td>4 (9.3)</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>Improvement of 1 class</td>
<td>27 (81.8)</td>
<td>29 (67.4)</td>
<td>36 (64.3)</td>
</tr>
<tr>
<td>No improvement</td>
<td>6 (18.2)</td>
<td>10 (23.3)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Change in quality of life</td>
<td>-3±17</td>
<td>-10±18</td>
<td>-16±20</td>
</tr>
<tr>
<td>Change in 6MHW distance</td>
<td>27±56</td>
<td>27±64</td>
<td>67±75</td>
</tr>
</tbody>
</table>

**Abbreviations as in Table 1.**

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assessed offline in a blinded fashion and therefore less subjected to placebo effect. The latter is commonly seen in symptomatic assessment adopted in device trials. Of particular importance, LV reverse remodeling is a predictor of favorable long-term outcome in the treatment of HF [12,22]. A recent meta-analysis which included 25 drug or device (CRT exclusively) therapy and 88 mortality plus remodeling studies, reported that an absolute increase in the mean LVEF of 5% and a per 10 ml reduction in the mean LVESV from baseline were predictors of a lower mortality [22]. Based on these information, the extent of LV reverse remodeling and the responder rate defined by the change in LVESV or LVEF were compared in the current study.

In early animal and human studies, the increase in LVEF caused by chronic intermittent CCM therapy (i.e. CCM signal delivery of 3–6 hours per day for 2–3 months) was observed, though LV reverse remodeling was not designed as a primary endpoint [6,23,24]. Imai et al. conducted a randomized, controlled study in heart failure dogs which firstly described the reduction in LVESV with gain in LVEF after 3 months in the CCM-treated group [5]. In a human study, CCM therapy resulted in a reduction of the mean LVESV by 11.5% and an absolute increase in the mean LVEF by 5% when assessed by three-dimensional echocardiography [10]. Although LV reverse remodeling has been commonly observed in many clinical trials of CRT, data are limited for CCM [11,25]. The present cohort study is the first comparison between CCM and CRT on the degree of clinical and echocardiographic improvement with CRT serving as the standard device therapy for drug-refractory HF.

In contrast to CRT that corrects systolic electromechanical dysynchrony commonly observed in HF patients with prolonged QRS duration, CCM provokes an increase of intracellular calcium that leads to the enhancement of cardiac contractility [2-4]. In patients with a narrow QRS complex who were not candidates of CRT according to the current guideline, CCM therapy resulted in the improvement of myocardial systolic function in both septal and LV free walls [10]. This concerted force in the LV not only enhances systolic function, but also reduces mitral regurgitation, and is likely linked to the normalization of gene and protein over-expressions involved in the pathologic process of HF [5]. However, the most interesting finding of the present study is that CCM patients did not respond as well as CRT patients with a QRS duration >150 ms in terms of the degree of LV reverse remodeling. Although our study was not envisaged to explore the reasons for the difference observed, we postulate that electromechanical delay-induced LV adverse remodeling and systolic dysfunction is a largely reversible condition. This is in contrast to patients with a narrow QRS complex and absence of LV dyssynchrony in whom HF signifies a more severe or a late stage disease with extensive myocyte loss and myocardial scarring. In other words, for the similar severity of cardiac remodeling in HF patients, the CCM recipients had structural damage as a main substrate of HF, while the CRT recipients had both structural and functional substrates in whom the latter was induced by electromechanical delay [26-28]. This may also explain why patients with a wider QRS duration of >150 ms showed a greater volumetric response after CRT than those with a borderline wide QRS duration of 120–150 ms. In fact, electromechanical delay as a reversible disease is also evident in recent multicenter trials of CRT for NYHA class I and II patients in whom both LV reverse remodeling and improved mortality/HF hospitalization were observed [29,30]. Sixteen clinical non-responders to CRT in a pilot study received CCM and showed improvement of LV volume and LVEF [31], however, there is no evidence that the reverse would work for CCM non-responders.

4.1. Limitations of the study

Firstly, this observational study was not a true head-to-head comparison of the effects of CCM and CRT in the three cohorts of HF
patients, even if most of their baseline clinical and demographic characteristics were similar. Therefore, the three groups might not be entirely comparable or it could have been complicated by some additional uncertainties, such as the means and the extent of revascularization, the presence of regional and global myocardial functional reserve. Secondly, the study would be more comprehensive and persuasive if a control group with only optimal medical therapy was included but it is difficult to deny suitable patients therapy with CRT in view of its proven benefits. Thirdly, the follow-up duration was relatively short, therefore, neither the late effect on LV reverse remodeling nor the long-term prognosis after CCM were observed. Although this single-center experience indicates a promising role of CCM as a new alternative therapy, more multicenter longitudinal studies with hard endpoints, besides surrogate variables, are necessary to establish the value of this new technology.

5. Conclusion

CCM appeared to exert a similar LV reverse remodeling response to CRT for HF patients with a mildly prolonged QRS complex, but was less effective than CRT for patients with a very wide QRS. Further studies are warranted to explore the relationship between LV reverse remodeling and long-term clinical outcome in CCM recipients.

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