

ORIGINAL RESEARCH

Impact of Cardiac Contractility Modulation on Left Ventricular Global and Regional Function and Remodeling

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OBJECTIVES This study aimed to evaluate the impact of cardiac contractility modulation (CCM) on left ventricular (LV) size and myocardial function.

BACKGROUND CCM is a device-based therapy for patients with advanced heart failure. Previous studies showed that CCM improved symptoms and exercise capacity; however, comprehensive assessment of LV structure, function, and reverse remodeling is not available.

METHODS Thirty patients (60 ± 11 years, 80% male) with New York Heart Association (NYHA) functional class III heart failure, ejection fraction $<35\%$, and QRS <120 ms were assessed at baseline and 3 months. LV reverse remodeling was measured by real-time 3-dimensional echocardiography. Using tissue Doppler imaging, the peak systolic velocity (S_m) and peak early diastolic velocity (E_m) were calculated for LV function, while the standard deviation of the time to peak systolic velocity (T_s -SD) and the time to peak early diastolic velocity (T_e -SD) were calculated for mechanical dyssynchrony.

RESULTS LV reverse remodeling was evident, with a reduction in LV end-systolic volume by $-11.5 \pm 10.5\%$ and a gain in ejection fraction by $4.8 \pm 3.6\%$ (both $p < 0.001$). Myocardial contraction was improved in all LV walls, including sites remote from CCM delivery (all $p < 0.05$); hence, the mean S_m of 12 (2.2 ± 0.6 cm/s vs. 2.5 ± 0.7 cm/s) or 6 basal LV segments (2.5 ± 0.6 cm/s vs. 3.0 ± 0.7 cm/s) were increased significantly (both $p < 0.001$). In contrast, CCM had no impact on regional or global E_m (2.9 ± 1.3 cm/s vs. 2.9 ± 1.1 cm/s), whereas T_s -SD (28.2 ± 11.2 ms vs. 27.9 ± 12.7 ms) and T_e -SD (30.0 ± 18.3 ms vs. 30.1 ± 20.7 ms) remained unchanged (all $p = \text{NS}$). Mitral regurgitation was reduced ($22 \pm 14\%$ vs. $17 \pm 15\%$, $p = 0.02$). Clinically, there was improvement of NYHA functional class ($p < 0.001$) and 6-min hall walk distance ($p = 0.015$). A 24-h Holter monitor showed that premature ventricular contractions were not increased during CCM.

CONCLUSIONS CCM improves both global and regional LV contractility, including regions remote from the impulse delivery, and may contribute to LV reverse remodeling and gain in systolic function. Such improvement is unrelated to diastolic function or mechanical dyssynchrony. (J Am Coll Cardiol Img 2009;2:1341–9) © 2009 by the American College of Cardiology Foundation

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Many patients with advanced heart failure (HF) are refractory to optimal standard medical therapy. This has given rise to development and testing of a host of new device-based therapies (1). One more recent and potentially broadly applicable treatment under investigation is cardiac contractility modulation (CCM) electrical signals (2,3). CCM signals are relatively high-voltage electrical impulses applied to the myocardium during the absolute refractory period. These signals do not initiate a new contraction or modify activation sequence as is the case with other therapies such as cardiac resynchronization therapy (CRT) (4). Rather, CCM signals are intended to enhance systolic function of the failing myocardium (5–8). Results of recent clinical studies suggest that CCM therapy is safe and improves exercise tolerance and quality of life in patients with HF (3,9–11) without increasing myocardial oxygen consumption (12). Recent studies in animal models and patients with HF indicate that a novel mechanism underlying these effects is normalized expression of genes known to be pathologically up- or down-regulated in HF (8,13).

Despite consistent findings concerning effects on exercise tolerance and quality of life, findings have been inconsistent with regard to the effect of CCM on left ventricular (LV) structure and function (10,11). Use of 2-dimensional (2D) echocardiography for such assessments is associated with significant variability, especially in the context of multicenter studies, even when a core laboratory is used. In contrast, real-time 3-dimensional (3D) echocardiography offers the opportunity for significantly more accurate and reproducible assessments, and reduces the need for large sample size (14). Furthermore, the potential mechanisms of how CCM may affect LV function have not been evaluated in previous studies. In particular, whether CCM would enhance only septal function where the 2 electrodes are implanted, or whether they impact LV free-wall function and the synchrony of mechanical contraction, are unknown. Therefore, the purpose of this study was to test the impact of CCM on LV size and global and regional myocardial function by real-time 3D echocardiography and tissue Doppler imaging.

years, 80% male) who received CCM treatment with an Optimizer III System (IMPULSE Dynamics, Inc., Orangeburg, New York). Patients were included if they had an ejection fraction <35%, New York Heart Association (NYHA) functional class III who remained symptomatic despite optimal medical therapy, and not eligible for CRT. The major exclusion criteria included permanent or persistent atrial fibrillation, peak $\dot{V}O_2 < 9$ ml/kg/min, patients who had an aortic or tricuspid mechanical prosthetic valve, patients with QRS duration >120 ms, hospitalization within 1 month for acute exacerbation of HF, revascularization within 1 month, or acute myocardial infarction within 3 months of study entry.

Baseline testing included echocardiography with real-time 3D echocardiography and tissue Doppler imaging, Minnesota Living with Heart Failure Questionnaire (MLWHFQ), 6-min hall walk test (6MHW) and 24-h Holter monitor. Patients who met the inclusion criteria were implanted with an Optimizer III System (IMPULSE Dynamics, Inc.). Details of the System implant have been provided previously (12). In brief, 2 right ventricular electrodes were placed at the anterior and inferior septal regions, respectively, for delivery of CCM, while a right atrial lead was placed at the right atrial appendage only for sensing the P-wave. Devices were programmed to deliver CCM signals 5 h per day (5 1-h periods distributed equally over the 24 h of the day). Patients were seen in follow-up after 3 months of CCM therapy, during which baseline tests were repeated. The study protocol was approved by the ethics committee of the institution, and written informed consent was obtained from all the patients.

Echocardiography. Standard echocardiography with Doppler measurements was performed. Doppler echocardiography was performed to assess LV diastolic function by interrogation of transmitral and pulmonary venous flow patterns. Left ventricular diastolic function and cardiac output were assessed by pulse-wave Doppler echocardiography (15). Diastolic function was graded as normal, abnormal relaxation, pseudonormal filling pattern, or restrictive filling pattern according to the established criteria (16). The rate of systolic pressure rise (+dP/dt) was estimated from the continuous-wave Doppler mitral regurgitation velocity curve (17). Myocardial performance index was also calculated by dividing the sum of isovolumic contraction and relaxation periods by the ejection period (18). Mitral regurgitation was quantified by the area of the

ABBREVIATIONS AND ACRONYMS

CCM = cardiac contractility modulation

CRT = cardiac resynchronization therapy

Em = peak early diastolic velocity

HF = heart failure

LV = left ventricular

MLWHFQ = Minnesota Living with Heart Failure Questionnaire

Sm = peak systolic velocity

Te-SD = standard deviation of the time to peak myocardial early diastolic velocity

Ts-SD = standard deviation of the time to peak systolic velocity

METHODS

Patients and study protocol. The present study enrolled 30 consecutive patients (mean age 60 ± 11

regurgitant jet measured by color Doppler expressed as a percentage of left atrial area in the apical 4-chamber view; the average of the results of at least 3 consecutive beats in sinus rhythm was taken for this parameter. The doctors who performed echocardiographic examinations were unaware of the treatment status of CCM. Furthermore, as CCM was delivered intermittently (5 h/day), the follow-up echocardiography was performed at the time of no active CCM signals delivered in order to maintain the blinding of image acquisition.

Real-time 3D echocardiography. Real-time 3D echocardiography was performed in the apical 4-chamber view by acquiring pyramidal full-volume images of the LV with a matrix-array transducer (X3-1, 1.9/3.8 MHz, iE33, Philips, Andover, Massachusetts). The image was adjusted to optimize the orthogonal 2D and then 3D image qualities with modified gain settings and compression controls as well as depth and lateral gain compensation to optimize full-volume acquisition. Patients were instructed to hold their breath to minimize artifacts induced by breathing during full-volume acquisition, which was triggered to the R-wave on the electrocardiogram (ECG) of every cardiac cycle, resulting in a total acquisition time of 4 heart beats. LV full-volume images with clear endocardial borders were stored digitally and transferred to a workstation for offline analysis (19-24). Quantitative analysis of 3D echocardiography images were performed offline in a blinded fashion by dedicated software (Q-Lab 6.0, Philips). In our echocardiographic core laboratory, blinding of data was maintained by scrambling echocardiographic examinations of all the time points for all the patients in a random order. Also, doctors who analyzed echocardiographic data were not involved in clinical management or follow-up of the patients, and therefore, they were totally unaware of the treatment status. During offline analysis, from the automatically cut planes that consisted of nonforeshortened end-diastolic apical 2- and 4-chamber views, 5 anatomic points were manually defined that included 2 points to identify the mitral valve annulus in each of the 2 apical views and 1 point to identify the apex in either view. A detection procedure was followed by the automated software to trace the LV endocardial border according to the preset mathematical model. The same procedure was repeated in the end-systolic frame. The surface detection could be edited manually if tracings were suboptimal. Thus, time-volume curves were derived from regional volumetric data of 17 myocardial segments accord-

Table 1. Baseline Clinical Characteristics of Patients Who Received CCM (n = 30)

Age (yrs)	60 ± 11
Sex	
Male	80%
Female	20%
Etiology	
Ischemic	50%
Nonischemic	50%
NYHA functional class III	100%
QRS duration (ms)	99 ± 15
LV ejection fraction (%)	29.0 ± 6.5
Vo ₂ max (ml/kg/min)	15.9 ± 4.7
ICD	6.7%
Diuretics	66.7%
ACEI or ARB	83.3%
Beta-blocker	73.3%
Aldactone	13.3%
Digoxin	6.7%

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCM = cardiac contractility modulation; ICD = implantable cardioverter-defibrillator; LV = left ventricular; NYHA = New York Heart Association; Vo₂ max = maximal oxygen consumption.

ing to American Society of Echocardiography classification (6 basal, 6 middle, and 5 apical segments), and from which the LV end-diastolic and -systolic volumes and ejection fraction were derived. Interobserver and intraobserver variability for measurement of LV ejection fraction was assessed in 15 randomly selected patients; these were 6.7% and 5.0%, respectively.

Tissue Doppler imaging. Color-coded tissue Doppler imaging was performed from the 3 standard apical views (apical 4-, 2-, and 3-chamber views) to assess LV long-axis function (Vivid 7, Vingmed-General Electric, Horten, Norway) as previously described (25). Images were optimized for pulse

Table 2. Comparison of Clinical Status Before and 3 Months After CCM Therapy

	Baseline	3 Months	p Value
Heart rate (beats/min)	77 ± 15	74 ± 12	0.257
24-h PVC	1,259 ± 2,109	1,440 ± 1,522	0.337
Systolic blood pressure (mm Hg)	120 ± 22	122 ± 23	0.594
Diastolic blood pressure (mm Hg)	75 ± 13	75 ± 15	0.881
NYHA functional class (% patients)			
II	—	83	<0.001
III	100	17	
MLWHF quality of life score	23 ± 19	20 ± 18	0.577
6-min hall walk (m)	331 ± 85	358 ± 83	0.015
Vo ₂ max (ml/kg/min)	15.9 ± 4.7	14.3 ± 4.6	0.059
Maximal exercise (METs)	4.5 ± 1.4	4.0 ± 1.3	0.060

MET = metabolic equivalent; MLWHF = Minnesota Living With Heart Failure; PVC = premature ventricular contraction; other abbreviations as in Table 1.

repetition frequency, color saturation, and sector size and depth to achieve the highest possible frame rate of >100 Hz. At least 5 consecutive beats were stored, and the images were analyzed offline with the aid of a customized software package (EchoPac PC SW-only, version 6.1.1, Vingmed-General Electric). Myocardial velocity curves were reconstituted offline using the 6-basal and 6-mid segmental model, which consisted of septal, lateral, anteroseptal, posterior, anterior, and inferior segments at both basal and mid-levels in the left ventricle (25,26). The basal segments were sampled just above the mitral annulus level, and the middle segments were sampled at the mid-level of the LV. Markers with valve opening and closing events would appear on the ECG recordings during offline analysis. To assess regional systolic function, the

peak systolic velocities during the ejection phase (S_m) of individual segments were measured, and global LV systolic function was defined as the mean of the 6 basal and 12 LV segmental S_m values (Mean S_m -6 and Mean S_m -12, respectively). Similarly, regional diastolic function was measured as the peak early diastolic velocity (E_m) of each individual segment, and global LV diastolic function was defined by the mean 6 basal and 12 LV segmental E_m values (Mean E_m -6 and Mean E_m -12, respectively).

To assess systolic dyssynchrony, we calculated the standard deviation of the time to peak myocardial systolic velocity during ejection phase of all the 12 LV segments (T_s -SD). Also, the maximal delay in T_s was presented in each of the 3 apical views. For diastolic dyssynchrony, the standard deviation of the time to peak myocardial early diastolic velocity of the 12 LV segments (T_e -SD) was calculated. These time domain variables were measured relative to the timing of the QRS complex (25,27). The interobserver and intraobserver variabilities for measuring dyssynchrony were compared in 60 consecutive measurements and were found to be 4.7% and 3.2%, respectively (26).

Statistics. Data were analyzed using a statistical software program (SPSS for Windows, version 13.0.1, SPSS Inc., Chicago, Illinois). Paired sample t test or Wilcoxon matched-pairs signed rank test was used when appropriate for comparisons of continuous or categorical variables between baseline and follow-up. Linear regression was employed to investigate the correlation between pairs of parametric variables. Comparison of nonparametric data was performed by Pearson chi-square test. The results were expressed as mean \pm SD. A p value of <0.05 was considered statistically significant.

RESULTS

Patient baseline characteristics are summarized in Table 1. The mean QRS duration was 99 ± 15 ms. About one-half of patients had ischemic etiology of HF. The mean LV ejection fraction was $29.0 \pm 6.5\%$. **Clinical assessment of CCM therapy.** There was significant improvement of NYHA functional class after 3 months of CCM treatment, with an average decrease of almost 1 class (Table 2). The 6MHW distance also increased significantly by an average of nearly 30 m. However, the improvement of the MLWHFQ score was not significant. The 24-h Holter monitoring showed that there was no significant change in the number of premature ven-

Table 3. Comparison of Global LV Function Before and 3 Months After CCM Therapy by Echocardiography

	Baseline	3 Months	p Value
Systolic function			
LV ejection fraction (%)	29.0 \pm 6.5	33.1 \pm 6.5	<0.001
LV end-systolic volume (ml)	115 \pm 35	103 \pm 37	<0.001
LV end-diastolic volume (ml)	159 \pm 40	150 \pm 40	0.002
LV end-systolic sphericity index	1.77 \pm 0.24	1.88 \pm 0.30	0.008
LV end-diastolic sphericity index	1.66 \pm 0.20	1.72 \pm 0.21	0.015
Cardiac output (ml/min)	2.9 \pm 1.1	3.3 \pm 1.0	0.03
Mitral regurgitation (% LA area)	22 \pm 14	17 \pm 15	0.032
LV +dP/dt (mm Hg/s)	736 \pm 112	882 \pm 128	0.010
MPI	0.72 \pm 0.26	0.62 \pm 0.16	0.01
Mean S_m -6 (cm/s)	2.5 \pm 0.6	3.0 \pm 0.7	<0.001
Mean S_m -12 (cm/s)	2.2 \pm 0.6	2.5 \pm 0.7	<0.001
Diastolic function			
Mitral E velocity (m/s)	0.68 \pm 0.27	0.64 \pm 0.25	0.383
Mitral A velocity (m/s)	0.61 \pm 0.26	0.65 \pm 0.26	0.248
Mitral E/A ratio	1.6 \pm 1.5	1.6 \pm 1.7	0.733
LV filling time (ms)	403 \pm 125	417 \pm 107	0.403
Mitral velocity time integral (cm)	13.8 \pm 3.5	14.7 \pm 3.7	0.04
LV filling pattern (% patients)			
Abnormal relaxation pattern	30	40	0.014
Pseudonormal filling pattern	27	37	
Restrictive filling pattern	43	23	
Septal annulus E' velocity (cm/s)	3.5 \pm 1.1	3.8 \pm 1.3	0.067
E/E'	21.2 \pm 11.7	18.3 \pm 10.0	0.043
Mean E_m -6 (cm/s)	3.3 \pm 1.5	3.3 \pm 1.3	0.910
Mean E_m -12 (cm/s)	2.9 \pm 1.3	2.9 \pm 1.1	0.827
Mean A_m -6 (cm/s)	3.1 \pm 1.5	3.5 \pm 1.6	0.013
Mean A_m -12 (cm/s)	2.6 \pm 1.2	2.9 \pm 1.3	0.005

A_m -6 = mean myocardial late diastolic velocity of the 6 basal LV segments; A_m -12 = mean myocardial late diastolic velocity of the 6 basal, 6 mid LV segments; +dP/dt = rate of systolic pressure rise; E_m -6 = mean myocardial early diastolic velocity of the 6 basal LV segments; E_m -12 = mean myocardial early diastolic velocity of the 6 basal, 6 mid LV segments; E' = myocardial early diastolic velocity at septal mitral annulus; LA = left atrial; MPI = myocardial performance index; S_m -6 = mean myocardial systolic velocity of the 6 basal LV segments; S_m -12 = mean myocardial systolic velocity of the 6 basal, 6 mid LV segments; VTI = velocity-time integral; other abbreviations as in Table 1.

tricular contractions after CCM, indicating no proarrhythmic effect.

Global assessment of LV function and reverse remodeling. Using real-time 3D echocardiography, there was significant reduction of LV end-systolic volume with an average of $-11.5 \pm 10.5\%$ ($p < 0.001$) (Table 3) (Figs. 1A and 1B). The LV end-diastolic volume was also reduced by $-5.5 \pm 8.0\%$ ($p = 0.002$), and LV ejection fraction increased by $4.8 \pm 3.6\%$ (absolute percentage point increase) ($p < 0.001$). Improvement of LV systolic function was corroborated by tissue Doppler imaging, which showed a significant increase in the mean Sm value of the 6 basal LV segments ($p < 0.001$) (Figs. 2A to 2F) and mean Sm value of the 12 LV segments ($p < 0.001$), which are markers for global LV systolic function. There was also improvement of cardiac output ($p = 0.03$), $+dP/dt$ ($p = 0.01$), and myocardial performance index ($p = 0.01$). Other parameters that were improved after CCM included sphericity index ($p = 0.008$) and mitral regurgitation ($p = 0.032$) (Table 3).

Doppler assessment of diastolic function did not reveal significant changes of conventional indices, including E velocity, A velocity, and E/A ratio (Table 3). However, LV diastolic pressure was reduced after CCM as reflected by the reduction of E/E' ratio ($p = 0.043$). This was also supported by the lower prevalence of restrictive filling pattern after CCM ($Z = -2.460$, $p = 0.014$). However, tissue Doppler imaging revealed that early diastolic function remained unchanged as reflected by the mean 6 basal and 12 LV segment Em values (Table 3, Figs. 2A to 2F).

Assessment of regional LV function and systolic dyssynchrony. Tissue Doppler imaging assessment of regional systolic function, i.e., Sm, was performed at the basal segments of all the 6 LV walls. This included septal and lateral walls in the 4-chamber view, anterior and inferior walls in the 2-chamber view, as well as anterior-septal and posterior walls in the 3-chamber view. As shown in Table 4, there were significant increases in Sm of all the LV walls (all $p < 0.05$), with a statistically nonsignificant trend for improvement in the septal wall ($p = 0.06$).

In contrast to the uniform improvement of regional systolic function, regional assessment of early diastolic function by tissue Doppler imaging (i.e., Em) did not show any evidence of increase after CCM (Table 4).

At baseline, 8 patients (27%) had significant LV dyssynchrony by Ts-SD measurement, and this

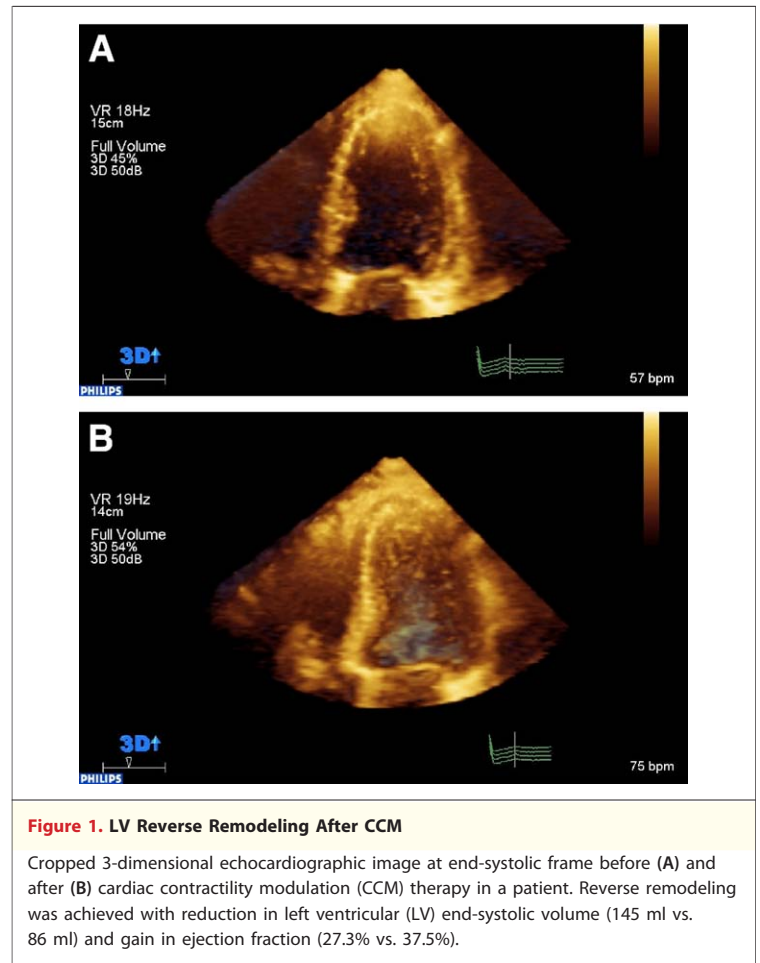
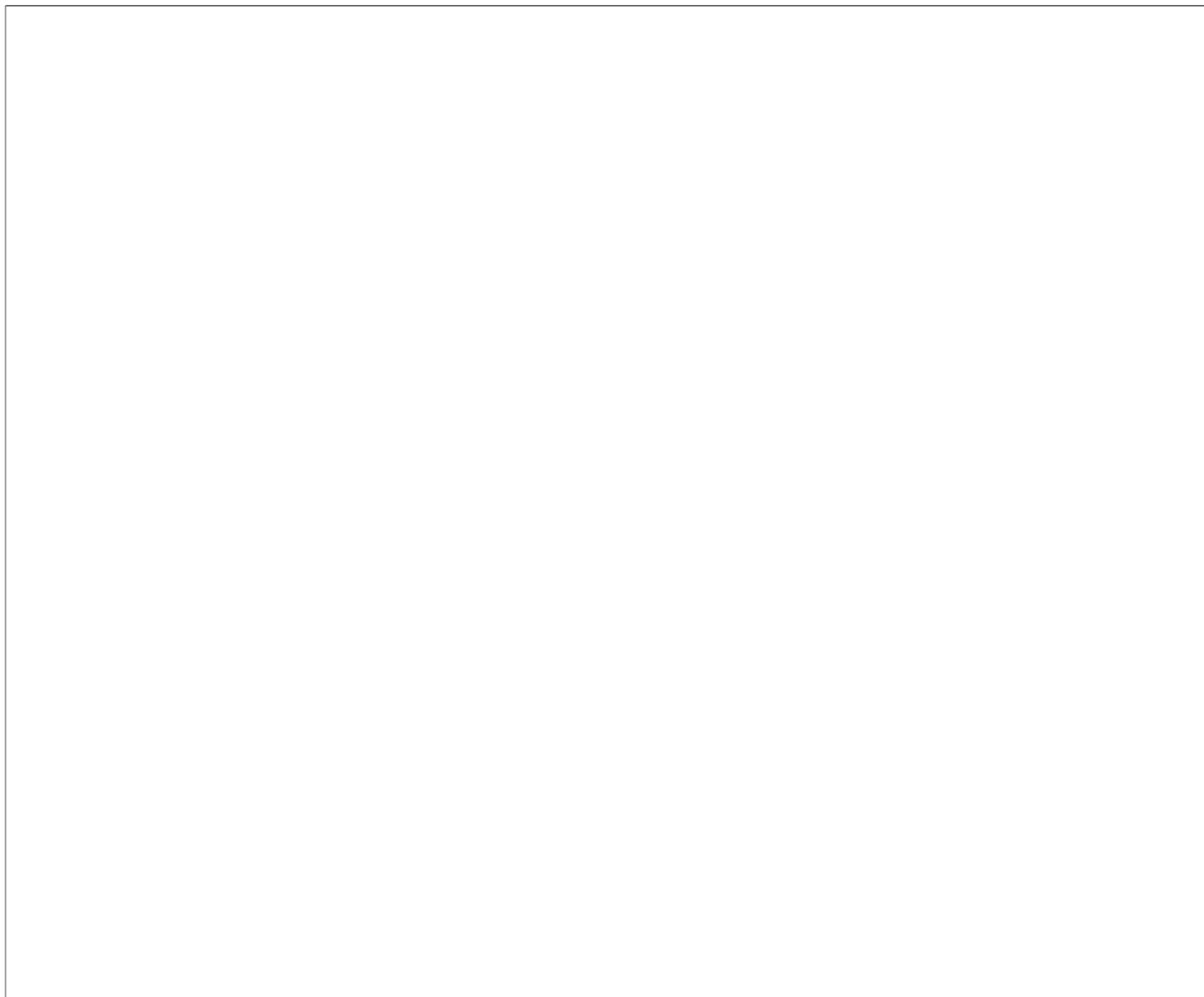


Figure 1. LV Reverse Remodeling After CCM
Cropped 3-dimensional echocardiographic image at end-systolic frame before (A) and after (B) cardiac contractility modulation (CCM) therapy in a patient. Reverse remodeling was achieved with reduction in left ventricular (LV) end-systolic volume (145 ml vs. 86 ml) and gain in ejection fraction (27.3% vs. 37.5%).

happened in 9 patients (30%) at 3-month follow-up. In addition, there were no changes in Ts-SD and other indices of systolic dyssynchrony, including opposite wall delay between baseline and 3-month follow-up (all $p > 0.05$). Similarly, index of diastolic dyssynchrony (i.e., Te-SD) was unchanged throughout the study period.

DISCUSSION

In patients receiving treatment with CCM for 3 months, there was improvement of LV systolic function as evidenced by an increase in ejection fraction measured using real-time 3D echocardiography and systolic contractility by tissue Doppler imaging, which resulted in LV reverse remodeling. These favorable changes were related to augmentation of systolic function uniformly in all regions of the LV, not just limited to the septal wall where CCM signals were delivered. Furthermore, mitral regurgitation was reduced. LV diastolic function was unaffected by CCM, and there was

**Figure 2. Impact of CCM on Systolic versus Diastolic Function**

Tissue Doppler imaging of apical 4-chamber (A and B), 2-chamber (C and D), and 3-chamber (E and F) views showing myocardial velocities before (A, C, and E) and after (B, D, and F) cardiac contractility modulation (CCM) therapy in the same patient as in Figure 1. At 3 months, the mean value of the peak myocardial systolic velocity (S_m) (arrows) of the 6 basal segments was improved (3.0 cm/s vs. 3.9 cm/s), whereas that of the peak early diastolic velocity (E_m) (arrowheads) was not (4.0 cm/s vs. 3.5 cm/s).

no evidence that CCM impacted on systolic or diastolic dyssynchrony.

Improvement of LV systolic function and LV reverse remodeling after CCM. Despite recent studies that reported improvement of symptoms and exercise capacity, whether CCM would induce favorable changes in cardiac structure and function was largely unknown. Results of multicenter trials have been mixed (10,11); however, the accuracy of M-mode measurement of dilated ventricles and with regional wall dyskinesia (e.g., in coronary heart disease) introduces a lot of variability, and results have therefore been questioned. Real-time 3D

echocardiography has been validated to be highly accurate and reproducible in assessing LV volume and ejection fraction, with values reflecting true measurements when compared with cardiac magnetic resonance and CT scan (14). Furthermore, real-time 3D echocardiography is much more accurate than 2D echocardiography and far superior to M-mode methods for such purposes. Our study employed real-time 3D echocardiography and reported an absolute gain in ejection fraction of $4.8 \pm 3.6\%$, whereas LV end-systolic volume reduced by $11.5 \pm 10.5\%$ following treatment with CCM after 3 months.

In this study, we made use of tissue Doppler imaging to assess long-axis systolic function by measuring Sm, which had been previously validated as a marker of LV contractility. Therefore, the increase of the averaged Sm in both 6 basal segments and 12 LV segments confirmed that the therapeutic effect of CCM was conveyed by enhancing LV intrinsic contractility. As a result, it would augment coaptation of the mitral valve and therefore decrease the amount of mitral regurgitation. As a consequence of better forward ejection of blood, the volume unloading effect and the alleviation of mitral regurgitation, LV reverse remodeling, and reduction of LV filling pressure were observed. The latter was confirmed by the observed reduction of E/E'.

Regional systolic versus diastolic function and mechanical synchrony after CCM. Mechanistic studies will provide insight into how CCM improves LV function. We observed that CCM did not just augment contractility at the septal and adjacent walls where the 2 electrodes were placed; rather, systolic function was enhanced in the entire LV including the free-wall segments. Therefore, in the long run, the concerted force in all 6 regions of the LV would contribute to the improvement of LV global systolic function, resulting in LV reverse remodeling and reduction of mitral regurgitation. These findings are completely consistent with a recent report concerning CCM-induced reverse molecular remodeling (8). When HF was experimentally induced in animals, there was a switch in expression of a host of genes from a normal adult genotype to a fetal genotype indicative of myocardial pathology. In such animals, Imai et al. (8) showed that within hours of initiating CCM signal delivery, there was a reversion back towards a normal genotype only in the region of the heart where signals were delivered. However, following 3 months of therapy, gene expression improved locally as well as in regions remote from the site of signal delivery (8). This prior finding, combined with the present findings of improved performance in all regions of the heart, indicates that although signal delivery is local, global benefits are achieved in the long run.

Three additional interesting findings were observed in the current study. First, there was no evidence of pro-arrhythmic effect of CCM as our patients showed a trend for the number of premature ventricular contractions observed during 24-h Holter monitoring to decrease following the 3-month treatment period. Second, despite improvement of global LV systolic function, CCM

Table 4. Improvement in Regional Myocardial Contraction But Not Relaxation After CCM Therapy Defined by Tissue Doppler Imaging

	Baseline	3 Months	p Value
Systolic function			
Sm, basal septal (cm/s)	2.8 ± 0.9	3.1 ± 0.9	0.064
Sm, basal lateral (cm/s)	2.4 ± 1.0	2.9 ± 1.1	0.005
Sm, basal anterior (cm/s)	2.3 ± 0.9	2.8 ± 1.1	0.024
Sm, basal inferior (cm/s)	2.9 ± 0.9	3.3 ± 0.9	<0.001
Sm, basal anteroseptal (cm/s)	2.2 ± 0.9	2.8 ± 0.8	<0.001
Sm, basal posterior (cm/s)	2.5 ± 0.9	3.0 ± 1.0	0.001
Diastolic function			
Em, basal septal (cm/s)	3.4 ± 1.9	3.1 ± 1.6	0.219
Em, basal lateral (cm/s)	3.5 ± 2.1	3.6 ± 2.3	0.815
Em, basal anterior (cm/s)	3.3 ± 2.0	3.5 ± 1.7	0.559
Em, basal inferior (cm/s)	3.4 ± 1.5	3.5 ± 1.5	0.570
Em, basal anteroseptal (cm/s)	2.5 ± 1.4	2.8 ± 1.5	0.191
Em, basal posterior (cm/s)	3.7 ± 2.3	3.2 ± 1.7	0.059
Am, basal septal (cm/s)	3.6 ± 1.9	3.9 ± 2.1	0.152
Am, basal lateral (cm/s)	2.4 ± 1.6	2.7 ± 1.6	0.105
Am, basal anterior (cm/s)	2.7 ± 1.7	3.3 ± 1.6	0.015
Am, basal inferior (cm/s)	3.9 ± 2.0	4.3 ± 2.0	0.140
Am, basal anteroseptal (cm/s)	2.9 ± 1.5	3.2 ± 1.7	0.050
Am, basal posterior (cm/s)	3.0 ± 1.6	3.2 ± 1.7	0.369
Dyssynchrony			
Ts-SD (ms)	28.2 ± 11.2	27.9 ± 12.7	0.809
Septal to lateral wall delay in Ts (ms)	47.9 ± 29.2	46.1 ± 32.0	0.741
Anterior to inferior wall delay in Ts (ms)	45.2 ± 27.0	43.5 ± 28.7	0.645
Anteroseptal to posterior wall delay in Ts (ms)	36.2 ± 34.2	35.5 ± 38.7	0.908
Te-SD (ms)	30.0 ± 18.3	30.1 ± 20.7	0.943

Am = myocardial late diastolic velocity at the time of atrial contraction; Em = myocardial early diastolic velocity; Sm = myocardial systolic velocity; Te-SD = standard deviation of the time to peak myocardial early diastolic velocity of the 12 left ventricular segments; Ts-SD = the standard deviation of the time to peak myocardial systolic velocity of the 12 left ventricular segments; Ts = time to peak myocardial systolic velocity; other abbreviations as in Table 1.

exerted no direct effect on active diastolic function. Despite the fact that early diastolic function is an energy-consuming process that involves the reuptake of intracellular calcium in addition to the passive recoil, CCM does not appear to play a role in modulating ventricular diastolic function. Third, the augmentation of global LV function was not explained by changes in mechanical synchrony since neither systolic nor diastolic synchrony was changed by CCM, though the prevalence of LV dyssynchrony was relatively low in these patients at baseline. This further supports the notion that the improved global function is likely a result of improved myocyte systolic function. This is in contrast to CRT in which the improvement of systolic function is largely related to the alleviation of systolic dyssynchrony (27). Thus, because the mechanisms are completely different, the effects of CCM can be additive to those of CRT, as shown previously (7,28). Finally, this finding also addresses

concerns that local application of CCM places undue stress on myocardium remote from the site of signal delivery, which could actually have the potential to adversely affect function in those areas (6); this was evidently not the case.

The clinical improvement of symptoms and exercise capacity in our study was comparable to those observed in previous multicenter trials (10). However, this was not the focus of the present study, since it was a small, unblinded study in which measures of patient symptoms and exercise tolerance were subject to placebo effect. This might also have explained the lack of improvement in quality of life assessment in the present study. Of note, the mean MLWHFQ score of our patients was relatively low, which rendered further improvement after CCM a technical challenge.

One limitation of the present study is the relatively short duration (3 months) of follow-up. Results of 1 prior clinical trial suggests that the clinical effect of CCM builds over time (10), so it might be expected that even more significant effects could be observed over longer periods of follow-up. Also, our study did not include a control group for comparison. However, given the results of patients in the placebo arm who

received CRT, such as in the CARE-HF (Cardiac Resynchronization in Heart Failure) study (29), no changes in LV volume and ejection fraction would have been expected after follow-up for 3 months. Furthermore, the blinding of data acquisition and offline analysis would have minimized the bias during interpretation of echocardiographic results.

CONCLUSIONS

Three months of treatment with CCM signals improved global LV systolic function by means of augmenting intrinsic contractility in all regions of the LV, resulting in reverse remodeling and reduction of mitral regurgitation. On the other hand, CCM did not affect global or regional LV diastolic function, and it had no impact on the degree of synchrony of myocardial contraction. Additional studies are underway to assess the long-term clinical impact of CCM.

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REFERENCES

- Mancini D, Burkhoff D. Mechanical device-based methods of managing and treating heart failure. *Circulation* 2005;112:438-48.
- Burkhoff D, Ben-Haim SA. Nonexcitatory electrical signals for enhancing ventricular contractility: rationale and initial investigations of an experimental treatment for heart failure. *Am J Physiol Heart Circ Physiol* 2005;288:H2550-6.
- Lawo T, Borggrefe M, Butter C, et al. Electrical signals applied during the absolute refractory period: an investigational treatment for advanced heart failure in patients with normal QRS duration. *J Am Coll Cardiol* 2005;46:2229-36.
- Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
- Brunckhorst CB, Shemer I, Mika Y, Ben Haim SA, Burkhoff D. Cardiac contractility modulation by non-excitatory currents: studies in isolated cardiac muscle. *Eur J Heart Fail* 2006; 8:7-15.
- Mohri S, He KL, Dickstein M, et al. Cardiac contractility modulation by electric currents applied during the refractory period. *Am J Physiol Heart Circ Physiol* 2002;282:H1642-7.
- Pappone C, Rosanio S, Burkhoff D, et al. Cardiac contractility modulation by electric currents applied during the refractory period in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 2002;90:1307-13.
- Imai M, Rastogi S, Gupta RC, et al. Therapy with cardiac contractility modulation electrical signals improves left ventricular function and remodeling in dogs with chronic heart failure. *J Am Coll Cardiol* 2007;49:2120-8.
- Pappone C, Augello G, Rosanio S, et al. First human chronic experience with cardiac contractility modulation by non-excitatory electrical currents for treating systolic heart failure: mid-term safety and efficacy results from a multicenter study. *J Cardiovasc Electrophysiol* 2004; 15:418-27.
- Neelagaru SB, Sanchez JE, Lau SK, et al. Nonexcitatory, cardiac contractility modulation electrical impulses: feasibility study for advanced heart failure in patients with normal QRS duration. *Heart Rhythm* 2006;3:1140-7.
- Borggrefe MM, Lawo T, Butter C, et al. Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure. *Eur Heart J* 2008;29:1019-28.
- Butter C, Wellnhofer E, Schlegl M, Winbeck G, Fleck E, Sabbah HN. Enhanced inotropic state of the failing left ventricle by cardiac contractility modulation electrical signals is not associated with increased myocardial oxygen consumption. *J Card Fail* 2007;13:137-42.
- Butter C, Rastogi S, Minden HH, Meyhofer J, Burkhoff D, Sabbah HN. Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure. *J Am Coll Cardiol* 2008;51:1784-9.
- Sugeng L, Mor-Avi V, Weinert L, et al. Quantitative assessment of left ventricular size and function: side-by-side comparison of real-time three-dimensional echocardiography and computed tomography with magnetic resonance reference. *Circulation* 2006;114:654-61.
- Yu CM, Sanderson JE, Shum IO, et al. Diastolic dysfunction and natriuretic peptides in systolic heart failure. Higher ANP and BNP levels are associated with the restrictive filling pattern. *Eur Heart J* 1996;17: 1694-702.

16. Lester SJ, Tajik AJ, Nishimura RA, Oh JK, Khandheria BK, Seward JB. Unlocking the mysteries of diastolic function: deciphering the Rosetta Stone 10 years later. *J Am Coll Cardiol* 2008;51:679-89.
17. Bargiggia GS, Bertucci C, Recusani F, et al. A new method for estimating left ventricular dP/dt by continuous wave Doppler-echocardiography. Validation studies at cardiac catheterization. *Circulation* 1989;80:1287-92.
18. Tei C, Ling LH, Hodge DO, et al. New index of combined systolic and diastolic myocardial performance: a simple and reproducible measure of cardiac function—a study in normals and dilated cardiomyopathy. *J Cardiol* 1995;26:357-66.
19. Zhang Q, Yu CM, Fung JW, et al. Assessment of the effect of cardiac resynchronization therapy on intraventricular mechanical synchronicity by regional volumetric changes. *Am J Cardiol* 2005;95:126-9.
20. Kapetanakis S, Kearney MT, Siva A, Gall N, Cooklin M, Monaghan MJ. Real-time three-dimensional echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. *Circulation* 2005;112:992-1000.
21. Caiani EG, Corsi C, Zamorano J, et al. Improved semiautomated quantification of left ventricular volumes and ejection fraction using 3-dimensional echocardiography with a full matrix-array transducer: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr* 2005;18:779-88.
22. Jacobs LD, Salgo IS, Goonewardena S, et al. Rapid online quantification of left ventricular volume from real-time three-dimensional echocardiographic data. *Eur Heart J* 2006;27:460-8.
23. Mor-Avi V, Sugeng L, Weinert L, et al. Fast measurement of left ventricular mass with real-time three-dimensional echocardiography: comparison with magnetic resonance imaging. *Circulation* 2004;110:1814-8.
24. Gerard O, Billon AC, Rouet JM, Jacob M, Fradkin M, Allouche C. Efficient model-based quantification of left ventricular function in 3-D echocardiography. *IEEE Trans Med Imaging* 2002;21:1059-68.
25. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. *Heart* 2003;89:54-60.
26. Yu CM, Fung JW, Zhang Q, et al. Tissue Doppler imaging is superior to strain rate imaging and postsystolic shortening on the prediction of reverse remodeling in both ischemic and nonischemic heart failure after cardiac resynchronization therapy. *Circulation* 2004;110:66-73.
27. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;105:438-45.
28. Butter C, Meyhofer J, Seifert M, Neuss M, Minden HH. First use of cardiac contractility modulation (CCM) in a patient failing CRT therapy: clinical and technical aspects of combined therapies. *Eur J Heart Fail* 2007;9:955-8.
29. Ghio S, Freemantle N, Scelsi L, et al. Long-term left ventricular reverse remodeling with cardiac resynchronization therapy: results from the CARE-HF trial. *Eur J Heart Fail* 2009;11:480-8.

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