Cardiac Contractility Modulation by Electric Currents Applied During the Refractory Period in Patients With Heart Failure Secondary to Ischemic or Idiopathic Dilated Cardiomyopathy

Carlo Pappone, MD, PhD, Salvatore Rosanio, MD, PhD, Daniel Burkhoff, MD, PhD, Yuval Mika, DSc, Gabriele Vicedomini, MD, Giuseppe Augello, MS, Itzhak Shemer, MD, David Prutchi, DSc, Walid Haddad, PhD, Ricardo Aviv, DSc, Yehuda Snir, DSc, Itzhak Kronzon, MD, Ottavio Alfieri, MD, and Shlomo A. Ben-Haim, MD, PhD

We assessed the feasibility of cardiac contractility modulation (CCM) by electric currents applied during the refractory period in patients with heart failure (HF). Extracellular electric currents modulating action potential and calcium transients have been shown to potentiate myocardial contractility in vitro and in animal models of chronic HF. CCM signals were biphasic square-wave pulses with adjustable amplitude, duration, and time delay from sensing of local electric activity. Signals were applied to the left ventricle through an epicardial vein (in 12 patients) or to the right ventricular (RV) aspect of the septum endocardially (in 6 patients). Simultaneous left ventricular (LV) and aortic pressure measurements were performed using a Millar catheter (Millar Instruments, Houston, Texas). Hemodynamics during RV temporary dual-chamber pacing was regarded as the control condition. Both LV and RV CCM stimulation increased dP/dtmax to a similar degree (9.1 ± 4.5% and 7.1 ± 0.8%, respectively; p < 0.01 vs controls), with associated aortic pulse pressure changes of 10.3 ± 7.2% and 10.8 ± 1.1% (p < 0.01 vs controls). Regional systolic wall motion assessed quantitatively by color kinesis echocardiography was markedly enhanced near the CCM electrode, and the area of increased contractility increased 4.6 ± 1.2 segments per patient. In 6 patients with HF with left bundle branch block, CCM signals delivered during biventricular pacing (BVP) produced an additional 16.1 ± 3.7% increase in dP/dtmax and a 17.0 ± 7.5% increase in pulse pressure compared with BVP alone (p < 0.01). CCM stimulation in patients with HF enhanced regional and global measures of LV systolic function, regardless of the varied delivery chamber or whether modulation was performed during RV pacing or BVP. ©2002 by Excerpta Medica, Inc.

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The weakened contractility of failing cardiac myocytes is believed to result, in large part, from an abnormally low amount of calcium delivered to the myofilaments during each beat, independent of disease etiology.1,2 A means of increasing intracellular myofilaments during each beat, independent of abnormally low amount of calcium delivered to the sarcoplasmic reticulum calcium loading, thereby affecting the excitation–contraction coupling process.7 In vivo application of CCM signals has shown positive inotropic effects in either healthy canine hearts or dog models of chronic heart failure (HF).8,9 The present study first evaluated the feasibility of CCM stimulation in patients with chronic left ventricular (LV) systolic dysfunction due to dilated cardiomyopathy. To obtain insight into potential mechanisms relevant to clinical application, this study explored the influence of the varying CCM delivery ventricular chambers on hemodynamic and mechanical response, and evaluated the potential independent effect of altering myocardial function by CCM while enhancing contractile synchrony by simultaneous biventricular pacing (BVP) in patients with HF with complete left bundle branch block.

METHODS

Patient recruitment: The present study included patients with either ischemic or idiopathic dilated cardiomyopathy and ejection fraction ≤35%, who were
referred for an electrophysiologic study or implantation of a pacing device, and who were willing and able to provide written informed consent. Long-term HF medications were maintained at the time of the study, including digoxin, an angiotensin-converting enzyme inhibitor, diuretics, and β blockers. Patients with atrial fibrillation, frequent ventricular premature beats, class 3 or 4 angina, intravenous inotropic therapy, or an implanted pacemaker or defibrillator were excluded. The study was approved by the Ethics Committee of the San Raffaele University Hospital (Milan, Italy), and all patients provided informed consent.

**Procedures:** Patients were studied in the fasting, nonseated state. All procedures were carried out after performing the electrophysiologic study or before implantation of a pacing device. Patients were instrumented with a 5Fr dual-sensor micromanometer catheter (Millar Instruments, Houston, Texas) for the simultaneous measurement of LV and aortic pressures. Quadripolar leads were inserted into the right atrium and right ventricle for temporary dual-chamber (DDD) pacing (regarded as the control condition) and used because suboptimal local sensing stability with standard leads required use of the right ventricular (RV) pacing artifact as a reference signal to ensure CCM delivery during the refractory period. Pacing and sensing thresholds were determined according to standard procedures. Pacing output was set at a 1-ms pulse duration, at an amplitude 3 times the threshold, and using a pacing rate ≥20% of the intrinsic sinus rate. The atrioventricular delay was set 15% lower than the intrinsic PR interval to ensure continuous ventricular capture.

**CCM signal generator and delivery techniques:** By design, CCM stimulation is nonexcitatory and must be delivered within a precise time window of local refractoriness determined by local electric myocardial activation sensing. Such CCM signals are produced through a line-powered device equipped with a waveform generator triggered by local activation. The CCM current used in the present study was a biphasic, square-wave pulse 20 to 40 ms in duration, delivered 30 to 60 ms after detection of local activation (Figure 1). Over the range of CCM pulse durations and time delays tested, for analysis we considered the values that provided, in each patient, the greatest increase in dp/dt max. The amplitude of the signal was initially set at 10 mA and reduced by 2-mA steps if the stimulation caused chest discomfort in patients. If no symptoms occurred, the amplitude was increased stepwise up to 14 mA. Current delivery was coupled to sensed or paced events by adaptive CCM timing and safety algorithms, which inhibit signal generation when irregular activation is detected, so that CCM stimulation is suppressed on ectopic beats and resumed only after 3 consecutive normal beats.

There were 3 study protocols. In protocol 1, CCM signals were delivered to the left ventricle through an octapolar 3.3Fr Revelation electrophysiology catheter (Cardima, Freemont, California) and advanced through the coronary sinus into an epicardial vein (Figure 2). Of the 8 rings located on the lead (surface 10.3 mm², inter-electrode distance 2 mm), 2 were selected for sensing local electric activity and another 2 for delivering the CCM signal. In protocol 2, CCM signals were applied to the RV septum by a bipolar 8Fr electrophysiology catheter (Tendril DX 1388T, Pacesetter Inc., Sylmar, California), and the current was delivered from the lead tip (surface 8.5 mm²) to the ring electrode (34 mm² located 10 mm apart; Figure 2). Because this lead could not be used for sensing while delivering CCM, local sensing was provided by a coronary vein Revelation lead (Cardima) used as a reference after measuring the conduction delay between local activity detected from this lead and sensing from the endocardial RV CCM catheter during RV DDD pacing. In protocol 3, performed in patients with HF with complete left bundle branch block (QRS interval >150 ms) and LV end-diastolic diameter >55 mm, CCM was delivered to the left ventricle during simultaneous BVP performed from the same site to which CCM was applied using the setting configuration of protocol 1.

**Hemodynamic measurements:** Aortic and LV pressures, body surface electrocardiograms, local electric activity, and device performance data were recorded digitally at a sampling rate of 1 kHz. The following measurements were made off-line by custom software: aortic systolic and diastolic pressures, aortic pulse pressure, LV dp/dt max and LV dp/dt min by the method of Kass et al, and LV end-diastolic pressure. Pulse pressure was used as an index of ejection-phase systolic function, because at constant heart rate and vascular load, it directly correlates with cardiac output. Hemodynamic effects of signals during 15-

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**FIGURE 1. Timing of CCM signal relative to hemodynamic and electric events. Top to bottom: simultaneous recordings of LV and aortic (AoP) pressures, dp/dt, surface electrocardiogram (ECG), and endocardial electrograms from LV and RV leads. After detecting right atrial and RV activation, the CCM generator waits for detection of local activation of the left ventricle (‘local sense’) and delivers the signal after a preset delay for a specified duration and amplitude.**
minute periods of steady-state CCM stimulation have been reported. Consistency of the hemodynamic changes were assessed by repeating stimulation 3 times after 5 minutes of rest.

**Echocardiographic evaluation:** Protocols 1 and 2 included quantitative echocardiographic assessment of global LV function changes and the regional extent of CCM effects. Studies were performed with a Hewlett-Packard Sonos 5500 ultrasound system (Palo Alto, California) equipped with acoustic boundary detection and color kinesis. Color kinesis is a validated real-time echocardiographic technique that provides global and regional information on the magnitude and time of LV wall motion by tracking and color encoding endocardial motion throughout the cardiac cycle. Images were obtained from multiple views after the acoustic quantification system had been activated and gain controls were adjusted to optimize tracking of the endocardial border. Recordings were obtained starting 5 minutes from CCM initiation and were stored on a rewritable optic disk for off-line analysis performed by 2 operators blinded to the applied therapy. All reported values represent mean measurements from 5 cardiac cycles. End-systolic and end-diastolic color-encoded images were automatically analyzed by custom software. Regional function analysis was based on a standard segmentation model corresponding to the coronary perfusion territories. The magnitude of endocardial motion was expressed in terms of incremental LV fractional area change or fractional filling in percent of segmental and global end-diastolic area. The temporal patterns of endocardial motion were assessed using ejection and filling rates as a function of time, as well as mean ejection time and filling.

**Statistical analysis:** Data are expressed as mean ± SD. Analysis was performed using analysis of variance for multiple comparisons. To identify regions with greatest and least response to CCM as defined by echo color kinesis parameters, the Ward’s clustering algorithm was used. A p value <0.05 was considered significant.

**RESULTS**

Table 1 lists demographic and baseline hemodynamic data for the 24 patients enrolled in the study. Etiology of HF was ischemic in 9 patients (37%) and idiopathic in 15 (63%). On average, ejection fraction was 28 ± 6% and New York Heart Association class was 2.7 ± 0.6. As expected, average QRS duration was higher in protocol 3 patients. Indexes of isovolumetric (dP/dt_{max}) and ejection-phase (pulse pressure) systolic function decreased to a similar degree in patients from all 3 protocols.

**Effects of CCM stimulation in different chambers:** CCM pulse characteristics used for stimulation of the LV or RV septum are listed in Table 2. Similar CCM delay and duration settings were used in the 2 protocols. In protocol 1, 2 patients complained of chest discomfort at 10 mA, which was abolished by reducing amplitude to 8 mA in 1 patient, whereas in the other patient, a further reduction to 6 mA was necessary. In protocol 2, no symptoms occurred, and it was possible to use a 14-mA CCM signal in all patients. No patient developed any evidence of significant ventricular arrhythmias during CCM delivery in either protocol.

Hemodynamic parameters reached new steady-state values within 3 to 5 minutes from stimulation onset and were maintained during CCM application. Hemodynamics returned toward baseline using a similar time duration after CCM signal termination.

Hemodynamic measurements at the steady state are listed in Table 2. During CCM stimulation of the LV or RV septum, dP/dt_{max} increased significantly (p <0.01) by 9.1 ± 4.5% and 7.1 ± 8.8%, respectively, compared with control conditions, which had an associated pulse pressure increase of 10.3 ± 7.2% and 10.8 ± 1.1% (p <0.01). Although the average hemodynamic effects of CCM signals were comparable from both delivery chambers, all patients in protocol 2 had a dP/dt_{max} change >5%, whereas this occurred in 10 of 12 patients in protocol 1. Remarkably, these changes were able to offset the negative hemodynamic effects of RV DDD pacing that had occurred in 9 patients (patients 1, 3, 8, 9, 11, 13, 14, 16, and 17) who had a 9.2 ± 2.1% decrease in dP/dt_{max} or to induce a further systolic function increase in 3 patients (patients 5, 7, and 15) in whom RV pacing increased dP/dt_{max} by 7.7 ± 1.6% compared with normal sinus rhythm. The dP/dt_{min} improved by nearly 3% to 4% (p <0.01) with CCM delivery to either the LV or RV septum, but LV end-diastolic pressure did not change significantly.

Echo color kinesis analysis demonstrated an overall increase in the magnitude and velocity of contraction in both protocols, expressed by a significant increase in global LV fractional area change and peak ejection rate and shortening in time-to-peak ejection rate, although mean ejection time was not significantly influenced (Table 3). Regional systolic wall motion improved most impressively at sites near the CCM.
During RV DDD pacing and CCM application, demonstrated the same sequence of regional LV contraction of integrated fractional area change demonstrated the same sequence of regional LV contraction of integrated fractional area change (31 ± 5% end-diastolic area). The area of increased contractility as expressed by the number of segments in this cluster was equivalent to 4.6 ± 1.2 segments per patient, which indicated that contractile enhancement involved 29% of the left ventricle (16-segment model). By assessing each patient, correspondence analysis showed that segments in each cluster were contiguous and that the nonpropagatory nature of CCM. To identify the number of regions that were characterized by the greatest response, we used a clustering algorithm to simultaneously analyze the changes in 2 LV regional systolic function variables—namely, regional ejection rate and fractional area change. This analysis elicited 2 distinct clusters. The first was characterized by highest variation in regional ejection rate (1.12 ± 0.27 end-diastolic area/s) and regional fractional area change (31 ± 5% end-diastolic area). The area of increased contractility as expressed by the number of segments in this cluster was equivalent to 4.6 ± 1.2 segments per patient, which indicated that contractile enhancement involved 29% of the left ventricle (16-segment model). By assessing each patient, correspondence analysis showed that segments in each cluster were contiguous and that the first cluster included the region of the CCM electrode. Global LV diastolic function parameters were significantly improved with CCM delivery to the left ventricle but not to the RV septum. Although LV stimulation produced similar changes in regional filling fraction in regions.
near and remote from the CCM electrode, RV stimulation improved regional filling fraction only in the septal segments but not in remote regions (Table 3).

**CCM delivery during BVP:** After attainment of a steady state with BVP, CCM stimulation (amplitude 10.7 ± 1.6 mA, delay 43 ± 14 ms, duration 30 ms) was applied for 15 minutes. No ventricular arrhythmia occurred. As shown in Figure 4, dP/dt max and pulse pressure increased significantly and consistently with BVP (p = 0.01 for parameters), and a further significant (p = 0.0001 and p = 0.004, respectively) increase was associated with CCM application. Effects of BVP on diastolic function were modest, as dP/dt min varied by only −1.9 ± 8.1% and LV end-diastolic pressure by −5.4 ± 7.3% (p = NS, respectively). With adjunct CCM stimulation, a further decrease in end-diastolic pressure was observed (−0.3 ± 1.3%) and dP/dt min increased by 5.4 ± 11% (p = NS, respectively).

**DISCUSSION**

The present study demonstrated the feasibility of enhancing global LV performance by applying non-excitatory electric currents to a region of the ventricular myocardium. The CCM signals were shown to induce a 9% increase in dP/dt max and a 10% increase in aortic pulse pressure during epicardial delivery to the left ventricle. Comparable systolic enhancement was also obtained by applying the CCM current to the RV septum, raising the possibility that direct stimulation of the left ventricle may not be necessary to achieve significant benefits. In addition, we had no cases of chest discomfort with endocardial CCM application. This suggests that the right-sided approach may permit the use of greater current amplitudes, which have been shown to correlate with stronger contractile potentiation in experimental preparations.  

**Pathophysiologic mechanisms:** In the present study, quantitative echocardiographic analysis demonstrated a profound increase in regional contractility close to the site of CCM delivery. Mechanistically, demonstration of a prominent regional effect involving approximately 30% of the left ventricle suggests that improvement of global LV systolic function is secondary to specific changes in local contractility, rather than due to a nonselective artifact, such as nervous system activation. Given the nonexcitatory nature of CCM, contractile enhancement in nearby segments that are not effectively stimulated is probably due to local unloading or stretching phenomena (Frank-Starling mechanism). The possibility that a substantial role in mediating the inotropic effect is played by local catecholamine release due to stimulation of epicardial nerves during CCM delivery through a coronary vein seems unlikely, given the similar contractile effect achieved with RV septal stimulation from the endocardium. In our study, CCM has been shown to affect diastolic function as assessed by echo color kinesis. Regional filling fraction was improved significantly with both the right- and left-sided approach, but globally only the latter approach produced significant improvement. These findings suggest a different spatial distribution of CCM effects on LV diastolic properties. LV relaxation is known to be a nonuniform process, and its heterogeneity can be augmented by different disease states, which may have influenced our results.  

**Synergism of CCM and BVP:** Extensive evidence has accumulated indicating that BVP provides acute and long-term clinical benefits in selected patients with HF. The purpose of BVP is to restore homogeneity of cardiac contraction in patients with major intraventricular conduction delay. Therefore, unlike

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**TABLE 3** Indexes of Global and Regional LV Systolic and Diastolic Function Derived from Color Kinesis Echocardiography During CCM Delivery to the Left Ventricle (protocol 1) or RV Septum (protocol 2)

<table>
<thead>
<tr>
<th></th>
<th>Protocol 1</th>
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<th>Protocol 2</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>CCM</td>
<td>% Change</td>
<td>Control</td>
</tr>
<tr>
<td>Global systolic function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAC (% EDA)</td>
<td>23 ± 6</td>
<td>28 ± 5†</td>
<td>22 ± 5</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>Peak ejection rate (EDA/s)</td>
<td>1.21 ± 0.26</td>
<td>1.49 ± 0.33†</td>
<td>24 ± 3</td>
<td>1.18 ± 0.36</td>
</tr>
<tr>
<td>Time-to-peak ejection rate (ms)</td>
<td>102 ± 36</td>
<td>91 ± 33†</td>
<td>−11 ± 4</td>
<td>118 ± 26</td>
</tr>
<tr>
<td>Mean ejection time (ms)</td>
<td>141 ± 14</td>
<td>147 ± 18</td>
<td>4 ± 2</td>
<td>148 ± 18</td>
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<tr>
<td>Regional systolic FAC (% EDA)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CCM region*</td>
<td>21 ± 10</td>
<td>32 ± 12†</td>
<td>52 ± 14</td>
<td>24 ± 12</td>
</tr>
<tr>
<td>Remote regions</td>
<td>18 ± 9</td>
<td>22 ± 11</td>
<td>18 ± 12</td>
<td>23 ± 12</td>
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<tr>
<td>Global diastolic function</td>
<td></td>
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</tr>
<tr>
<td>Filling fraction (% EDA)</td>
<td>27 ± 9</td>
<td>35 ± 11†</td>
<td>30 ± 8</td>
<td>22 ± 10</td>
</tr>
<tr>
<td>Peak filling rate (EDA/s)</td>
<td>0.07 ± 0.06</td>
<td>0.11 ± 0.04†</td>
<td>57 ± 28</td>
<td>0.1 ± 0.2</td>
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<tr>
<td>Time-to-peak filling rate (ms)</td>
<td>0.9 ± 0.4</td>
<td>1.4 ± 0.6†</td>
<td>47 ± 19</td>
<td>1.2 ± 0.6</td>
</tr>
<tr>
<td>Mean filling time (ms)</td>
<td>210 ± 22</td>
<td>238 ± 29†</td>
<td>13 ± 4</td>
<td>220 ± 28</td>
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<tr>
<td>Regional diastolic filling fraction (% EDA)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>CCM region*</td>
<td>24 ± 11</td>
<td>29 ± 12†</td>
<td>21 ± 8</td>
<td>26 ± 10</td>
</tr>
<tr>
<td>Remote regions</td>
<td>19 ± 12</td>
<td>24 ± 18†</td>
<td>26 ± 12</td>
<td>24 ± 12</td>
</tr>
</tbody>
</table>

*CCM region was defined in protocol 1 on the basis of the coronary vascular distribution territories, and in protocol 2 by visualization of the CCM catheter tip by fluoroscopy and echocardiography.

†p < 0.05 versus control.

EDA = end-diastolic area; FAC = fractional area change.
CCM stimulation, this therapy does not affect myocardial contractility per se, but improves LV performance by making more efficient use of existing muscle strength. In terms of the magnitude of the hemodynamic benefits with BVP, increases in dP/dt_max and pulse pressure ranging from 13% to 20% and 7% to 15%, respectively, have been reported. These values are similar to those seen in the present study. Nevertheless, CCM application simultaneous to BVP in our study provided adjunct benefits, inasmuch as it produced an additional 16% increase in dP/dt_max and a 17% increase in pulse pressure. This result concretely raises the possibility that CCM technology in combination with BVP could enhance the efficacy of multisite pacing therapy for HF.

**Study limitations:** In the present study, CCM stimulation was performed during RV DDD pacing, which may improve or impair systolic and diastolic LV function in patients with HF and dilated cardiomyopathy. However, our data showed that CCM could either offset or enhance the effects of RV pre-excitation in a beneficial manner. This, added to the clear additional effects of CCM during BVP, suggests that the degree of improvement during normal sinus rhythm should be similar or greater than that observed during RV pacing, but this needs to be tested using active fixation leads providing optimal sensing and CCM delivery. Pacing was performed above the intrinsic sinus rate to avoid heart rate changes affecting the
Inotropic state, but this may have masked any CCM effects to enhance sympathetic activity and secondarily increase heart rate. The testing order of controls versus CCM was not randomized, thus carryover effects cannot be excluded. Lastly and importantly, great caution must be taken in drawing conclusions on whether CCM-induced hemodynamic improvements are sustainable in the long term.

Acknowledgment: We wish to express our appreciation to the patients and to the technicians and nurses of the electrophysiologic and cardiac pacing unit for their dedication and outstanding support.