## FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

# Electrical Signals Applied During the Absolute Refractory Period

## An Investigational Treatment for Advanced Heart Failure in Patients With Normal QRS Duration

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Cardiac resynchronization therapy has been shown to be an effective treatment for patients with systolic ventricular dysfunction, prolonged (>120 ms) QRS duration, and New York Heart Association (NYHA) functional class III or IV symptoms despite optimal medical therapy. However, studies show that a majority of heart failure patients have QRS duration <120 ms. We have been investigating the potential utility of cardiac contractility modulating (CCM) signals as a treatment option for such patients. Cardiac contractility modulating signals are non-excitatory signals applied during the absolute refractory period using a pacemaker-like device that connects to the heart with pacemaker leads. Acute studies carried out in animals and humans with heart failure suggest that CCM signals can enhance the strength of left ventricular contraction. Results of initial long-term studies designed mainly to demonstrate feasibility and provide preliminary indication of safety in patients with medically refractory NYHA functional class III heart failure are summarized. The results of these preclinical and clinical studies formed the basis for proceeding with two prospective, randomized clinical studies currently underway to definitively test the safety and efficacy of this treatment.     (J Am Coll Cardiol 2005;46:2229–36) © 2005 by the American College of Cardiology Foundation

The impact of biventricular pacing on ventricular contractile strength and clinical outcome when applied to patients with advanced heart failure and abnormally prolonged activation has been the topic of active research for over 10 years (1,2). Clinical studies have shown that this treatment, referred to as cardiac resynchronization therapy (CRT), improves patient symptoms, quality of life, exercise tolerance, and reduces hospitalizations (3,4). The degree of improvement in ventricular function (quantified by ejection fraction [EF]) amounts to an average ~4 percentage points, which is not apparent immediately, but which appears within six months of initiating therapy (5). Although use of QRS duration to predict which patients have mechanical dyssynchrony has

been reported as being less than perfect (6,7), and some studies suggest that resynchronization may not be the only mechanism leading to clinical improvement (8), QRS duration remains paramount in patient selection. Still, it is estimated that less than one-half of patients with heart failure have a prolonged QRS duration and would therefore be potentially eligible for treatment with CRT (9,10).

Accordingly, development of a device-based means of safely enhancing ventricular contractile strength in patients with normal activation sequence (i.e., normal QRS duration) who have advanced heart failure despite optimal medical therapy could have an important impact. This brief review summarizes initial results obtained with such a treatment currently undergoing investigation based on the application of cardiac contractility modulation (CCM) electrical impulses. The cellular basis for this treatment has been recently summarized (11,12). This review focuses on large animal and early clinical results.

## CCM CONCEPT

One cellular defect that underlies myocardial contractile dysfunction in heart failure is reduction in the peak and broadening of the time course of the intracellular calcium transient (13). Such abnormalities reflect heart failure-

associated changes in expression of genes encoding calcium-handling proteins and post-translational modification of their associated proteins. Several of the commonly discussed abnormalities include down-regulation of genes encoding for the sarcoplasmic reticulum adenosine triphosphate–dependent calcium pump (14–17), changes in expression and hypophosphorylation of phopholamban (16–21), altered regulation of the sodium-calcium exchanger (17,22,23), and hyperphosphorylation of the ryanodine release channel (24–26). Accordingly, it has been proposed that treatments aimed at improving the calcium transient in heart failure could be therapeutic (27).

Early studies of isolated cardiac muscle showed that use of voltage clamping techniques to modulate the amplitude and duration of membrane depolarization could modulate calcium entry and contractility in isolated papillary muscles (28–31). Increases in the duration and amplitude of depolarization have each been associated with increases in the strength of cardiac muscle contraction, which have been linked with increased calcium influx, calcium loading of the sarcoplasmic reticulum, and increased calcium release to the myofilaments. However, because voltage clamping is not applicable to the intact heart, this approach was never considered as a treatment option for heart failure. A conceptual breakthrough occurred with recognition and experimental demonstration in isolated superfused muscle strips that similar effects could be achieved when extracellular fields with relatively high current densities are applied over relatively long durations during the absolute refractory period (Fig. 1) (11). These so-called *CCM signals* contain ~150 times the amount of energy delivered in standard pacemaker impulse. These signals do not initiate the contraction, they do not recruit additional contractile elements, and there is no additional action potential (as would be observed with paired pacing or post-extra systolic potentiation). Cardiac contractility modulation signals are thus referred to as non-excitatory.

Borrowing from earlier published reports on voltage clamping (28–31), several studies were undertaken to investigate contributing mechanisms of the effects of CCM signals in isolated superfused muscles. Initial evidence suggested that CCM signals influence calcium cycling, thus enhancing the strength of the heart beat (11,32). Whether this mechanism is in effect during the intermediate (hours) or long term (days and beyond), signal application is currently not known and is the subject of ongoing research.

## CCM EFFECTS IN NORMAL AND HEART FAILURE ANIMALS

In vivo field stimulation of entire hearts of larger mammals is not feasible because of practical considerations related to power availability and nonspecific stimulation of other tissues (e.g., nerves, skeletal muscles, and so on). Studies were undertaken to understand the impact of regional CCM signal delivery on regional contractile function and to test the degree to which such signals could impact on global contractility (Fig. 2) (33). The results indeed showed that CCM signals impact on myocardial function in the region where they are applied (assessed by regional pressure-segment length loops), that these effects are significant enough to exert an influence on the strength of global contractility (as assessed by global pressure-volume relationships), and that the effects are additive when applied simultaneously to different regions of the heart.

More importantly, these signals have been shown to have a similar effect in animals with heart failure. In one
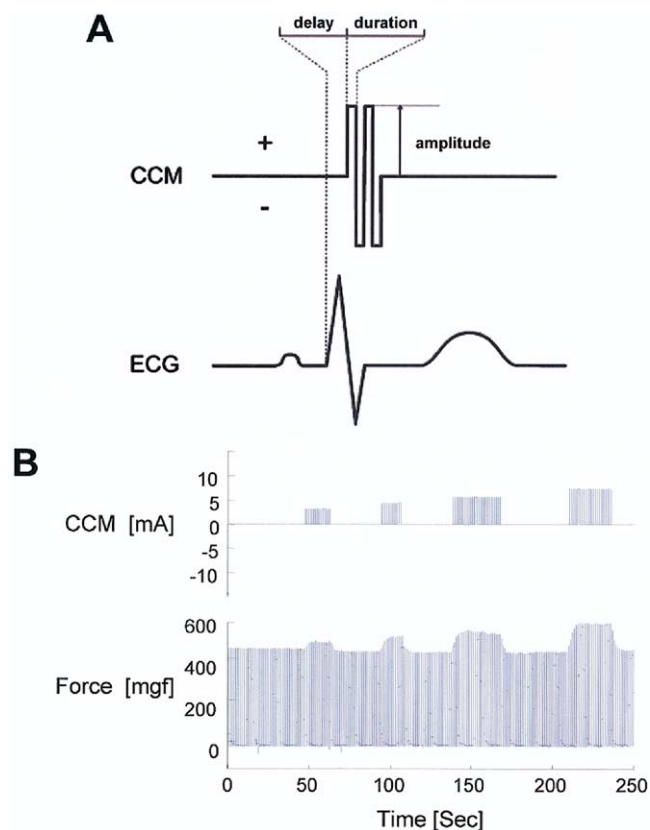


**Figure 1.** **(A)** Cardiac contractility modulating (CCM) signals employed in clinical study are biphasic pulses delivered after a defined delay from detection of local electrical activation. **(B)** Effects of CCM signals on isometric force measured from trabecular muscle of an end-stage failing heart obtained at heart transplant (11,12). ECG = electrocardiogram.
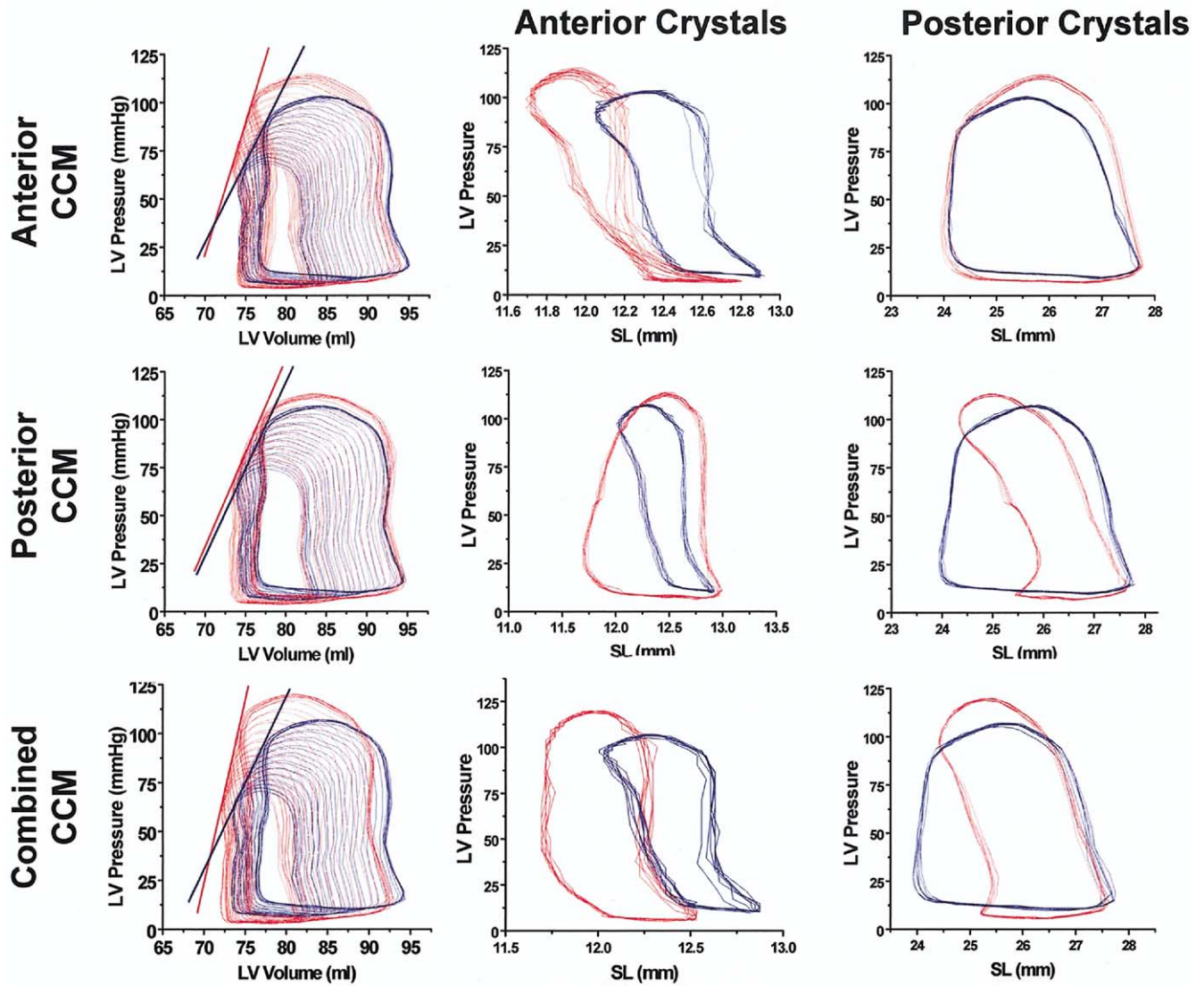
**Figure 2.** Effects of cardiac contractility modulating (CCM) signals on global function assessed by pressure-volume relations **(left column)** and on regional function in the anterior wall **(middle column)** and posterior wall **(right column)** assessed by pressure-segment length (SL) loops when signals are applied to the anterior wall **(top row)**, posterior wall **(middle row)**, and simultaneously to both walls **(bottom row)**. Baseline shown in **blue**; measurements during CCM signal application shown in **red**. LV = left ventricular. Used with permission from Mohri et al. (33).

series of experiments, heart failure was induced by multiple sequential intracoronary microembolizations until EF was ≤40% (34,35). Hemodynamic parameters and myocardial oxygen consumption ($MV_{O_2}$) were measured in an open-chest, anesthetized state, with epicardial electrodes used to administer CCM signals. Results of measured parameters are summarized in Table 1 (36). Heart rate and peak left ventricular (LV) pressure did not change significantly with CCM therapy. Acute CCM therapy tended to decrease LV end-diastolic pressure, which, after 2 h of continuous CCM therapy, was statistically significant. Left ventricular end-diastolic volume did not change with acute CCM therapy, but LV end-systolic volume decreased significantly after 1 h. Thus, LV EF increased significantly with CCM therapy as did cardiac output at both 1 and 2 h of CCM signal application. The improvement in LV systolic function

**Table 1.** Hemodynamic and Angiographic Measurements (Mean ± SEM)

|  | Baseline | 1 h of CCM | 2 h of CCM |
|---|---|---|---|
| Heart rate (beats/min) | 89 ± 3 | 98 ± 4 | 93 ± 6 |
| Systolic LV pressure (mm Hg) | 84 ± 4 | 81 ± 4 | 80 ± 4 |
| LV EDP (mm Hg) | 14 ± 2 | 12 ± 2 | 11 ± 1* |
| LV EDV (ml) | 55 ± 2 | 52 ± 2 | 53 ± 3 |
| LV ESV (ml) | 36 ± 2 | 31 ± 2* | 30 ± 2* |
| LV EF (%) | 34 ± 1 | 40 ± 1* | 42 ± 2* |
| Cardiac output (l/min) | 1.66 ± 0.04 | 2.01 ± 0.13* | 2.12 ± 0.12* |
| Total LV CBF (ml/min) | 78 ± 13 | 82 ± 21 | 89 ± 29 |
| $MV_{O_2}$ (μmol/min) | 213 ± 32 | 197 ± 56 | 209 ± 48 |
| LV efficiency (%) | 22 ± 4 | 33 ± 17 | 28 ± 5 |

*p < 0.05 vs. baseline.
  CBF = coronary blood flow; CCM = cardiac contractility modulation; EDP = end-diastolic pressure; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; LV = left ventricular; $MV_{O_2}$ = myocardial oxygen consumption.

seen in this study was accompanied by unchanged total LV coronary blood flow and unchanged $MV_{O_2}$.

## INITIAL CLINICAL STUDY OF ACUTE CCM SIGNALS

The initial clinical study of CCM signals involved short-term (10- to 30-min) CCM signal application using temporarily placed electrodes in patients with heart failure who had a clinical indication for an electrophysiology procedure (such as a CRT and/or implantable cardioverter-defibrillator [ICD], or a study for evaluation of ventricular or supraventricular arrhythmias) (37–39). This study involved patients with an average age of 60 ± 11 years with an average EF 28 ± 6%, having either ischemic or idiopathic cardiomyopathy. The findings showed the feasibility of delivering CCM treatment in humans and demonstrated that contractile performance could be enhanced. The signals were applied to patients with normal and prolonged QRS complexes, and similar acute effects were identified in both groups (Fig. 3). The data from all patients studied showed an average ~10% increase in $dP/dt_{max}$ that was independent of baseline QRS duration (Fig. 3A). In a subgroup of the patients with long QRS, CCM signals were also applied simultaneously with biventricular pacing; the effects on acute contractile performance as quantified by $dP/dt_{max}$ of CRT and CCM were shown to be additive in most patients (Fig. 3B) (38).
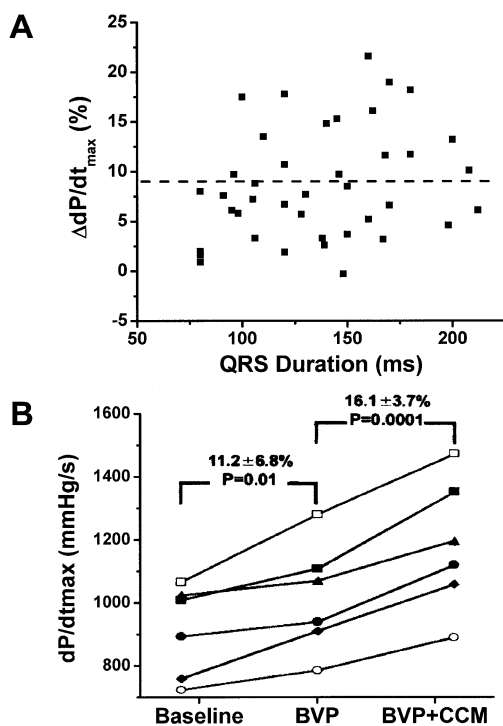


**Figure 3. (A)** Acute effects of cardiac contractility modulating (CCM) signals on $dP/dt_{max}$ in patients with heart failure. Average CCM effect **(dashed line)** was independent of QRS duration. **(B)** In patients with prolonged QRS duration, CCM effects were additive to those of biventricular pacing (BVP) **(B)** Reprinted from Pappone et al. (38) with permission from Excerpta Medica, Inc.

Another study examined the impact of acute CCM signal application on $MV_{O_2}$ (40). Patients were instrumented to measure coronary flow velocity in the left main artery; quantitative angiography was performed to measure left main diameter at the site of velocity measurement (for calculation of cross-sectional area). Coronary flow was therefore estimated as the product of velocity and cross-sectional area. Myocardial oxygen extraction was estimated from measurements of arterial and coronary venous blood $pO_2$ and hemoglobin content. Myocardial oxygen consumption, in turn, was estimated as the product of oxygen extraction and coronary flow. This study was performed in a group of 11 patients, 6 having idiopathic cardiomyopathy, and 5 having ischemic cardiomyopathy in whom EF averaged 26 ± 4% and peak $V_{O_2}$ averaged 13.9 ± 2.3 ml $O_2$/kg/min. The results showed that $MV_{O_2}$ was 13.6 ± 9.7 ml $O_2$/min at baseline versus 12.5 ± 7.2 ml $O_2$/min during CCM application (p = NS). This was in the setting of an average 8.8 ± 4.8% increase in $dP/dt_{max}$.

## DEVICE DESCRIPTION AND IMPLANTATION PROCEDURE IN HUMANS FOR ASSESSMENT OF LONG-TERM SAFETY AND EFFICACY

In the clinical setting, CCM signals are delivered to the heart by an implanted device that looks like a pacemaker and connects to the heart via standard commercially available pacing leads. The device, called the OPTIMIZER System (41), does not have pacing or antitachycardia therapy capabilities but is designed to work in concert with pacemakers and internal defibrillators. The originally investigated systems had a fixed battery, which, because of the high energy delivered with each CCM pulse, had longevity of six to eight months. More recently, a system with a rechargeable battery has been introduced. With this new system, the patient recharges the battery at home once per week via a transcutaneous energy transfer charging unit.

The implant procedure itself is also similar to that of a standard dual-chamber pacemaker. A pocket is generally made in the right subclavian region (a pacemaker/ICD usually residing on the left subclavian region), and three electrodes are introduced into the subclavian vein in a standard manner. One electrode is positioned in the right atrium and is used only for sensing atrial activity; this signal is used in an arrhythmia detection algorithm described below to inhibit CCM signal delivery during arrhythmias. The other two electrodes are positioned on the right ventricular septum. The right ventricular septum can be thought of as an extension of the LV epicardium. Positioning of the electrodes in this location obviates the need for a potentially lengthy procedure of coronary sinus cannulation to reach the LV epicardium proper, yet allows for CCM signals to influence LV contractile strength to the desired degree (38). To achieve the desired impact on LV performance, CCM signals are delivered through two electrodes.

**RAO**

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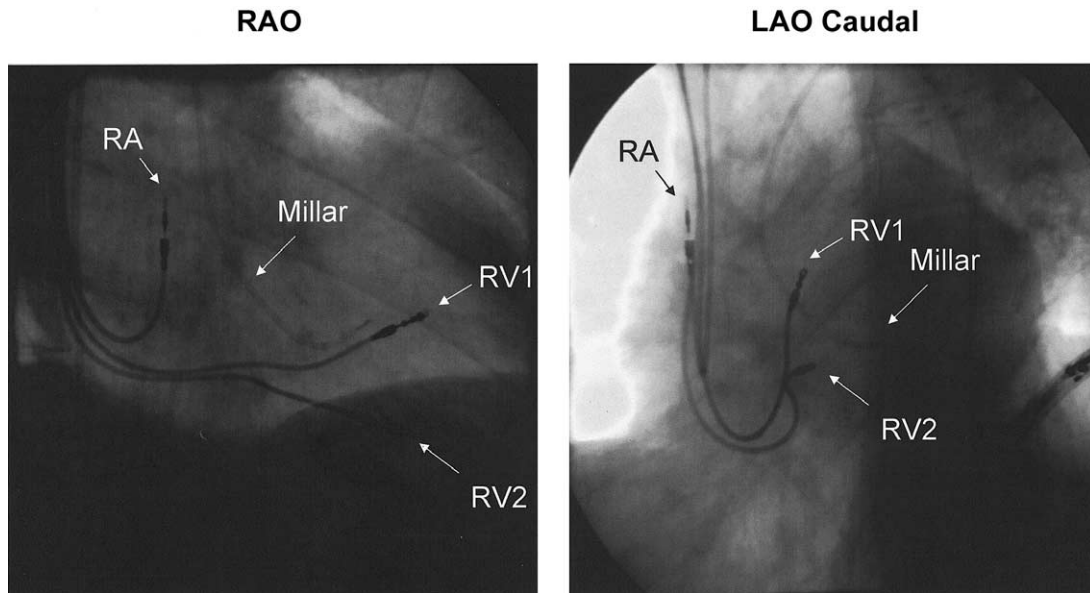


**Figure 4.** Right anterior oblique (RAO) and left lateral oblique (LAO) fluoroscopic images of electrode placement during OPTIMIZER System implant. One lead is placed in the right atrium (RA), and two leads are placed on the right ventricular septum (RV1, RV2) approximately mid-way between the base and apex, one near the anterior and one near the posterior interventricular groove. The LAO caudal view shows the electrode tips point toward the left side of the patient's body, into the septum. A micromanometer (Millar) is placed temporarily to measure physiologic response to acute cardiac contractility modulating signal application.

These electrodes are positioned under fluoroscopic guidance approximately half way between the base and apex, one ideally placed near the anterior interventricular groove and the other near the posterior groove (Fig. 4). In addition to fluoroscopy, proper electrode positioning is confirmed by measuring a physiologic response to acute CCM signal application through online assessment of changes in LV $dP/dt_{max}$ (measured via an LV Millar micromanometer, Millar Instruments, Houston, Texas). If initial electrode placement does not result in a specified increase in $dP/dt_{max}$, the electrodes are repositioned until such an effect is achieved. If the desired effect could not be achieved, the device was not implanted, and patients were withdrawn from the study in which they were enrolled. The estimated rate of patient withdrawal for this reason is ~5% to 10%.

The OPTIMIZER System parameters are set via a programmer that transcutaneously communicates with the implanted device. The OPTIMIZER System is designed to inhibit CCM pulse delivery on arrhythmias. This is to avoid the possibility that the signal might be delivered during the vulnerable period (e.g., on a T-wave), which could induce an arrhythmia. In the present device, this is achieved by delivering CCM signal only on normal sinus beats, which are defined as the detection of a P-wave followed by detection of electrical depolarization at the two right ventricular septal electrodes each within their own specified timing windows relative to the P-wave. The timing window for each electrode is programmed for each patient individually. A future device is planned that incorporates a more sophisticated arrhythmia detection algorithm that does not rely on P-wave detection and therefore could be used in patients with atrial fibrillation.

## LONG-TERM SIGNAL APPLICATION IN PATIENTS WITH NEW YORK HEART ASSOCIATION (NYHA) FUNCTIONAL CLASS III CHRONIC HEART FAILURE (CHF)

The initial experiences with long-term CCM signal applications were reported in two papers describing results obtained in patients with NYHA functional class III symptoms and QRS duration ≤120 ms (41,42). The studies described in these reports were unblinded, uncontrolled, treatment only, feasibility studies designed mainly to test the functionality of the OPTIMIZER System (41,42). The first of these papers described interim results of the initial experience with the system (42), whereas the second paper described the final results of a formal multicenter study (41). In the later study, the OPTIMIZER System was implanted in 23 patients with average age 62 ± 9 years who were primarily male (92%) and were split between idiopathic and ischemic cardiomyopathy (41% and 59%, respectively). Baseline EF averaged 22 ± 7%, and Minnesota Living With Heart Failure Questionnaire (MLWHFQ) score averaged 43 ± 22. Patients were well medicated with diuretics (88%), beta-blockers (88%), and angiotensin-converting enzyme inhibitors (100%). The study revealed that the device operated as intended, there was no change in ambient ectopy observed between baseline and eight weeks of treatment, and no overt safety concerns were revealed (Fig. 5). Additionally, improvements were reported in patient symptoms (assessed by NYHA functional class), quality of life (assessed by MLWHFQ), and EF (Fig. 6). Notably, the degree of improvement in EF reported in this study after eight weeks of treatment was comparable to those reported
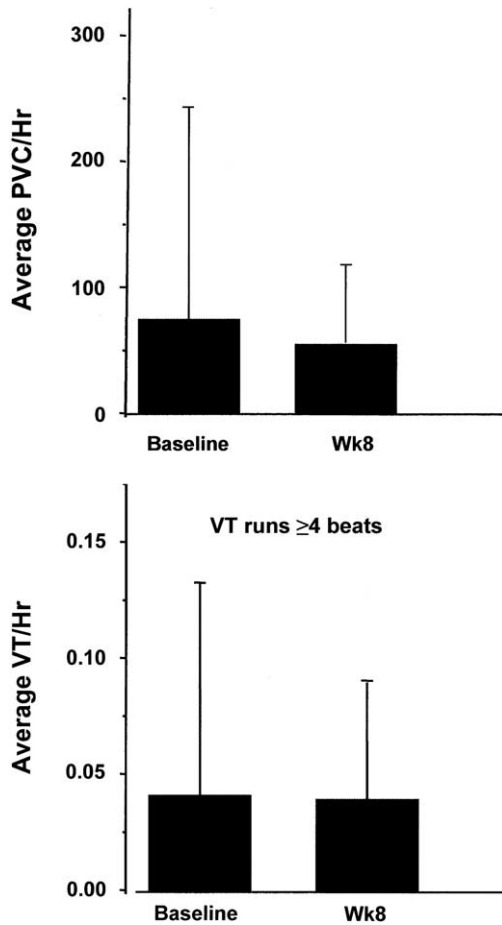
**Figure 5.** Holter monitor analysis available from the first 22 patients exposed to cardiac contractility modulating signals for eight weeks showed no significant change in ambient ectopy quantified by either the average total number of premature ventricular contractions (PVCs) per hour of the average number of runs of tachycardia consisting of four or more consecutive beats of ventricular tachycardia (VT) (41).

in atrial fibrillation or in patients with a large amount of ambient ectopy. Second, proper positioning of leads currently relies on detection of an acute rise in LV $dP/dt_{max}$. In current study protocols, the device is not implanted in patients in whom such a response cannot be demonstrated. This requirement is not meant to imply any expectation that acute hemodynamic response will predict long-term clinical improvement, only to ensure that the electrodes are in a position that can influence myocardium contributing to LV function. A simpler method of guiding and confirming proper lead positioning would be advantageous. Third, the previous version of the device (the OPTIMZIER II) had a
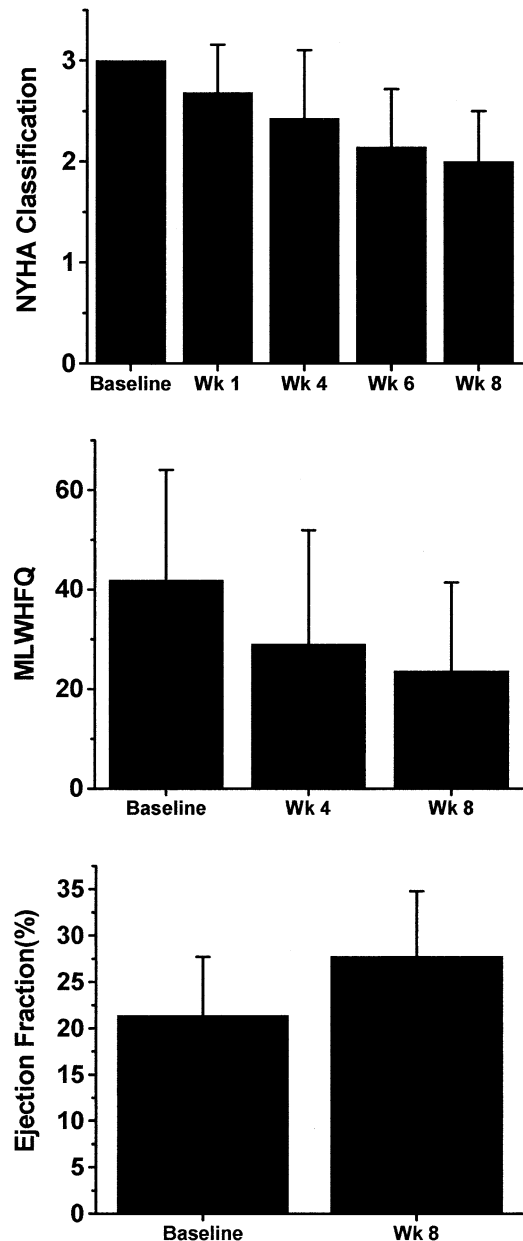
in response to CRT in patients with prolonged QRS duration.

To date, completed studies are non-randomized, non-blinded (therefore subject to placebo effect), and with small sample size. Two multicenter, randomized, controlled studies of CCM are currently underway (one in Europe and one in the U.S. being performed under an investigational device exemption from the U.S. Food and Drug Administration) to definitively test the safety and efficacy of CCM as a treatment for heart failure. The safety evaluations include examination of mortality, hospitalizations, potential proarrhythmic effects, signs of progressive heart failure, and overall incidence and severity of adverse events.

## POTENTIAL LIMITATIONS

Certain potential limitations evident at this early stage are noteworthy. First, the device being introduced in the currently running clinical studies (called the OPTIMIZER III) is designed to inhibit CCM delivery on arrhythmias and relies on detection of a P wave as part of the arrhythmia detection algorithm. Therefore, this device cannot be used



**Figure 6.** Results of a feasibility study suggest improvements over time in New York Heart Association (NYHA) functional classification, Minnesota Living With Heart Failure Questionnaire (MLWHFQ) score, and ejection fraction over the eight-week course of the study (41).

relatively short battery life. This limitation has been overcome in the OPTIMIZER III device with introduction of a transcutaneously rechargeable battery. Finally, some patients have experienced sensation with CCM signal delivery. Performance of the implant with patients in a non-sedated state is intended to minimize the incidence of this effect, but can still be reported.

## SUMMARY AND CONCLUSIONS

Studies of CCM signals performed in isolated muscle strips and in intact hearts of animals with CHF have suggested that these signals can enhance myocardial contractile strength. Cardiac contractility modulation signal delivery with a pacemaker-like device connected to the heart with standard pacing leads has been shown to be straightforward to implement clinically. Ongoing basic research focuses on new mechanisms by which myocardial properties can be influenced by CCM signals, particularly in the long-term setting. For example, results of preliminary studies in animals suggest that within 6 h of CCM signal delivery there are significant changes in myocardial gene expression (including a reversal of several aspects of the fetal gene program expressed in heart failure [43,44]), improved expression and phosphorylation of the sodium-calcium exchanger, phospholamban and connexin 43 (45–50). It is therefore possible that chronic effects may be independent of the acute effects discussed in the preceding text both in terms of their nature and underlying mechanisms.

Preliminary studies in patients have been encouraging. The overall safety and efficacy of this form of treatment are being tested in randomized, controlled clinical trials. If these studies show CCM treatment in patients with normal QRS duration to be as safe and effective as CRT in patients with prolonged QRS, a new, easily deployable treatment will be made available to patients with otherwise untreatable symptoms. Future studies could also evaluate whether CCM is effective in patients with wide QRS who declare themselves non-responsive to CRT or if combining CRT with CCM is more effective than CRT alone. Testing of these hypotheses would be facilitated by development of a single device that incorporates pacing, antitachycardia therapies, and CCM.

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## REFERENCES

1. Auricchio A, Sommariva L, Salo RW, Scafuri A, Chiariello L. Improvement of cardiac function in patients with severe congestive heart failure and coronary artery disease by dual chamber pacing with shortened AV delay. Pacing Clin Electrophysiol 1993;16:2034–43.
2. Auricchio A, Abraham WT. Cardiac resynchronization therapy: current state of the art: cost versus benefit. Circulation 2004;109: 300–7.
3. Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
4. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
5. St. John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985–90.
6. Kass DA. Ventricular resynchronization: pathophysiology and identification of responders. Rev Cardiovasc Med 2003;4 Suppl 2:S3–13.
7. Yu CM, Yang H, Lau CP, et al. Regional left ventricle mechanical asynchrony in patients with heart disease and normal QRS duration: implication for biventricular pacing therapy. Pacing Clin Electrophysiol 2003;26:562–70.
8. Morris-Thurgood JA, Turner MS, Nightingale AK, Masani N, Mumford C, Frenneaux MP. Pacing in heart failure: improved ventricular interaction in diastole rather than systolic re-synchronization. Europace 2000;2:271–5.
9. Sandhu R, Bahler RC. Prevalence of QRS prolongation in a community hospital cohort of patients with heart failure and its relation to left ventricular systolic dysfunction. Am J Cardiol 2004;93:244–6.
10. Shenkman HJ, Pampati V, Khandelwal AK, et al. Congestive heart failure and QRS duration: establishing prognosis study. Chest 2002; 122:528–34.
11. Burkhoff D, Shemer I, Felzen B, et al. Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo. Heart Fail Rev 2001;6:27–34.
12. 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 2005. In press.
13. Gomez AM, Valdivia HH, Cheng H, et al. Defective excitation—contraction coupling in experimental heart failure. Science 1997;276: 800–6.
14. Hasenfuss G, Reinecke H, Studer R, et al. Relation between myocardial function and expression of sarcoplasmic reticulum Ca2+-ATPase in failing and nonfailing human myocardium. Circ Res 1994;75:434–42.
15. Frank KF, Bolck B, Brixius K, Kranias EG, Schwinger RH. Modulation of SERCA: implications for the failing human heart. Basic Res Cardiol 2002;97 Suppl 1:I72–8.
16. Mishra S, Gupta RC, Tiwari N, Sharov VG, Sabbah HN. Molecular mechanisms of reduced sarcoplasmic reticulum Ca(2+) uptake in human failing left ventricular myocardium. J Heart Lung Transplant 2002;21:366–73.
17. O'Rourke B, Kass DA, Tomaselli GF, Kaab S, Tunin R, Marban E. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. Circ Res 1999;84:562–70.
18. Haghighi K, Gregory KN, Kranias EG. Sarcoplasmic reticulum Ca-ATPase-phospholamban interactions and dilated cardiomyopathy. Biochem Biophys Res Commun 2004;322:1214–22.
19. Frank K, Kranias EG. Phospholamban and cardiac contractility. Ann Med 2000;32:572–8.
20. Schmidt U, Hajjar RJ, Kim CS, Lebeche D, Doye AA, Gwathmey JK. Human heart failure: cAMP stimulation of SR Ca(2+)-ATPase activity and phosphorylation level of phospholamban. Am J Physiol 1999;277:H474–80.
21. Schwinger RH, Munch G, Bolck B, Karczewski P, Krause EG, Erdmann E. Reduced Ca(2+)-sensitivity of SERCA 2a in failing human myocardium due to reduced serin-16 phospholamban phosphorylation. J Mol Cell Cardiol 1999;31:479–91.
22. Studer R, Reinecke H, Bilger J, et al. Gene expression of the cardiac Na+ −Ca2+ exchanger in end-stage human heart failure. Circ Res 1994;75:443–53.
23. Heerdt PM, Holmes JW, Cai B, et al. Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. Circulation 2000;102:2713–9.
24. Marx SO, Reiken S, Hisamatsu Y, et al. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. Cell 2000;101:365–76.
25. Wehrens XH, Lehnart SE, Marks AR. Intracellular calcium release channels and cardiac disease. Annu Rev Physiol 2005;67:69–98.
26. Li Y, Kranias EG, Mignery GA, Bers DM. Protein kinase A phosphorylation of the ryanodine receptor does not affect calcium sparks in mouse ventricular myocytes. Circ Res 2002;90:309–16.

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JACC Vol. 46, No. 12, 2005
December 20, 2005:2229–36

27. Dorn GW, Molkentin JD. Manipulating cardiac contractility in heart failure: data from mice and men. Circulation 2004;109:150–8.
28. Wood EH, Heppner RL, Weidmann S. Inotropic effects of electric currents: 1. positive and negative effects of constant electric currents or current pulses applied during cardiac action potential. Circ Res 1969;24:409–45.
29. Wood EH, Heppner RL, Weidmann S. Inotropic effects of electric currents: 2. hypotheses: calcium movements, excitation-contraction coupling and inotropic effects. Circ Res 1969;24:409–45.
30. Antoni H, Jacob R, Kaufmann R. Mechanical response of the frog and mammalian myocardium to changes in the action potential duration by constant current pulses. Pflugers Arch 1969;306:33–57.
31. Kaufmann RL, Antoni H, Hennekes R, Jacob R, Kohlhardt M, Lab MJ. Mechanical response of the mammalian myocardium to modifications of the action potential. Cardiovasc Res 1971;1 Suppl 1:64–70.
32. Mohri S, Shimizu J, Mika Y, et al. Electric currents applied during the refractory period enhance contractility and systolic calcium in ferret. Am J Physiol Heart Circ Physiol 2002;284:1119–23.
33. 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.
34. Sabbah HN, Stein PD, Kono T, et al. A canine model of chronic heart failure produced by multiple sequential coronary microembolizations. Am J Physiol 1991;260:H1379–84.
35. Sabbah HN, Shimoyama H, Kono T, et al. Effects of long-term monotherapy with enalapril, metoprolol, and digoxin on the progression of left ventricular dysfunction and dilation in dogs with reduced ejection fraction. Circulation 1994;89:2852–9.
36. Sabbah HN, Imai M, Haddad W, et al. Non-excitatory cardiac contractility modulation electric signals improve left ventricular function in dogs with heart failure without increasing myocardial oxygen consumption (abstr). Heart Rhythm 2004;1:S181.
37. Pappone C, Vicedomini G, Loricchio ML, et al. First clinical experience demonstrating improvement of hemodynamic parameters in heart failure patients through the application of non-excitatory electrical signals (abstr). J Am Col Cardiol 2000;35 Suppl A:A229.
38. 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.
39. Pappone C, Vicedomini G, Salvati A, et al. Electrical modulation of cardiac contractility: clinical aspects in congestive heart failure. Heart Fail Rev 2001;6:55–60.
40. Butter C, Wellnhofer E, Schlegl M, Winbeck G, Burkhoff D, Fleck E. Enhanced inotropic state by cardiac contractility modulation signals is not associated with changes in myocardial oxygen consumption (abstr). Heart Rhythm 2004;1:S278.
41. Stix G, Borggrefe M, Wolpert C, et al. Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure. Eur Heart J 2004;25:650–5.
42. Pappone C, Augello G, Rosanio S, et al. First human chronic experience with cardiac contractility modulation by nonexcitatory electrical currents for treating systolic heart failure: mid-term safety and efficacy results from a multicenter study. J Cardiovasc Electrophysiol 2004;15:418–27.
43. Feldman AM, Weinberg EO, Ray PE, Lorell BH. Selective changes in cardiac gene expression during compensated hypertrophy and the transition to cardiac decompensation in rats with chronic aortic banding. Circ Res 1993;73:184–92.
44. Colucci WS. Molecular and cellular mechanisms of myocardial failure. Am J Cardiol 1997;80:15–25L.
45. Mishra S, Gupta RC, Haddad W, et al. Therapy with non-excitatory cardiac contractility modulation electrical signals partially restores MRNA expression of connexin 43 in left ventricular myocardium of dogs with heart failure (abstr). J Card Fail 2004;10:153.
46. Gupta RC, Mishra S, Rastogi S, et al. Short-term therapy with non-excitatory modulation electric signals increases phosphorylation of phospholamban in left ventricular myocardium of dogs with chronic heart failure (abstr). Eur Heart J 2004;25:1116.
47. Gupta RC, Mishra S, Rastogi S, et al. Non-excitatory cardiac contractility modulation electric signals normalize phosphorylation and expression of the sodium calcium exchanger in left ventricular myocardium of dogs with heart failure (abstr). Eur Heart J 2004;25:1116.
48. Rastogi S, Mishra S, Habib O, et al. Therapy with non-excitatory cardiac contractility modulation electric signals reverses the maladaptive fetal gene program in LV myocardium of dogs with heart failure (abstr). Circulation 2003;108:IV444.
49. Mishra S, Gupta RC, Rastogi S, Haddad W, Mika Y, Sabbah HN. Short-term therapy with nonexcitatory cardiac contractility modulation electric signals increases phosphorylation of phospholamban in left ventricular myocardium of dogs with chronic heart failure (abstr). Circulation 2004;110:III604.
50. Gupta RC, Mishra S, Sharad R, et al. Non-excitatory cardiac contractility modulation electric signals normalize phosphorylation and expression of the sodium calcium exchanger in left ventricular myocardium of dogs with heart failure (abstr). J Am Coll Cardiol 2005;45:151A.