

**You might find this additional information useful...**

---

This article cites 67 articles, 30 of which you can access free at:

<http://ajpheart.physiology.org/cgi/content/full/288/6/H2550#BIBL>

This article has been cited by 6 other HighWire hosted articles, the first 5 are:

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

C.-M. Yu, J. Y.-S. Chan, Q. Zhang, G. W.K. Yip, Y.-Y. Lam, A. Chan, D. Burkhoff, P.-W. Lee and J. W.-H. Fung

*J. Am. Coll. Cardiol. Img.*, December 1, 2009; 2 (12): 1341-1349.

[Abstract] [Full Text] [PDF]

**Cardiac contractility modulation in non-responders to cardiac resynchronization therapy**

H. Nagele, S. Behrens and C. Eisermann

*Europace*, December 1, 2008; 10 (12): 1375-1380.

[Abstract] [Full Text] [PDF]

**Cardiac Contractility Modulation Electrical Signals Improve Myocardial Gene Expression in Patients With Heart Failure**

C. Butter, S. Rastogi, H.-H. Minden, J. Meyhofer, D. Burkhoff and H. N. Sabbah

*J. Am. Coll. Cardiol.*, May 6, 2008; 51 (18): 1784-1789.

[Abstract] [Full Text] [PDF]

**Modulation of cardiac contractility. A potential treatment of heart failure?**

J. C. Daubert

*Eur. Heart J.*, April 2, 2008; 29 (8): 961-963.

[Full Text] [PDF]

**Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure**

M. M. Borggrefe, T. Lawo, C. Butter, H. Schmidinger, M. Lunati, B. Pieske, A. R. Misier, A. Curnis, D. Bocker, A. Remppis, J. Kautzner, M. Stuhlinger, C. Leclercq, M. Taborsky, M. Frigerio, M. Parides, D. Burkhoff and G. Hindricks

*Eur. Heart J.*, April 2, 2008; 29 (8): 1019-1028.

[Abstract] [Full Text] [PDF]

Medline items on this article's topics can be found at <http://highwire.stanford.edu/lists/artbytopic.dtl> on the following topics:

Biochemistry .. Angiotensin II  
Cell Biology .. Extracellular Space  
Oncology .. Aldosterone  
Oncology .. Heart Transplantation  
Immunology .. CD143  
Pharmacology .. Heart Diseases (Drug Development)

Updated information and services including high-resolution figures, can be found at:

<http://ajpheart.physiology.org/cgi/content/full/288/6/H2550>

Additional material and information about *AJP - Heart and Circulatory Physiology* can be found at:

<http://www.the-aps.org/publications/ajpheart>

---

This information is current as of November 21, 2010 .

## Nonexcitatory electrical signals for enhancing ventricular contractility: rationale and initial investigations of an experimental treatment for heart failure

MAJOR ADVANCES in pharmacological treatments for chronic heart failure in the setting of reduced ejection fraction have been made over the past two decades. Use of angiotensin-converting enzyme (ACE) inhibitors (19),  $\beta$ -blockers (45a, 58, 60), angiotensin II receptor type 1 blockers (65), and aldosterone inhibitors (66, 67) have each been shown to significantly improve survival in these patients. In a majority of patients, however, these treatments delay disease progression and only rarely reverse it to any substantial degree. As evidence, the number of hospitalizations for heart failure exacerbations continues to increase (3, 9), and a majority of patients will ultimately die of complications related to heart failure (11, 45a). Lack of a cure for heart failure and the large number of patients at risk, especially with the aging population, has fueled an intensive ongoing effort to learn more about pathophysiological mechanisms that will lead to the development of new treatments.

The major advances in pharmacological treatments noted above came with the recognition that the progressive ventricular dilation and deterioration of ventricular pump function characteristic of heart failure secondary to underlying molecular, cellular, biochemical, metabolic, and extracellular matrix abnormalities (collectively referred to as ventricular remodeling) are due to the pathologically elevated mechanical stresses on the myocardium [i.e., increased preload and afterload (7)] and to sustained neurohormonal and cytokine activation (42, 43, 54, 56). Recent studies of human hearts and myocardium obtained from patients requiring prolonged left ventricular (LV) assist device support before orthotopic heart transplantation have implicated specific aspects of the remodeling processes as being primarily governed by either neurohormonal or mechanical factors (7, 40). Myocardial unloading can be achieved pharmacologically by diuretics and afterload reducers such as ACE inhibitors, but the degree of unloading is limited by the need to maintain adequate blood pressure and cardiac output. Randomized studies have shown that pharmacological blockade of the key neurohormonal pathways interrupts the vicious cycle, retards progression, and improves survival. However, results of several recent trials suggest that attempts to block additional neurohormonal or cytokine pathways may be detrimental (18, 21, 44). This has led to the concept that we may have reached the limit to which neurohormonal and cytokine mechanisms can be blocked in heart failure (18, 20, 21, 44). If this is indeed the case, alternate approaches must be pursued. While the main targets for successful treatments have been the periphery, many investigators are revisiting strategies that directly improve ventricular pump function (25).

Early investigations of heart failure treatments explored direct pharmacological inotropic therapies. These approaches were shown to have an adverse effect on survival (26, 27, 55,

57, 59). The introduction of  $\beta$ -blockers, however, showed that the mechanism by which inotropy is achieved is important.  $\beta$ -Blockers, although negatively inotropic in the acute setting, induce positive inotropic actions when used chronically as evidenced by increases in ejection fraction and improved adrenergic responsiveness (10, 30). Although additional advances in pharmacological treatment for heart failure are anticipated, several device-based treatments intended to directly enhance ventricular function are in various stages of development.

### CARDIAC RESYNCHRONIZATION THERAPY

Cardiac resynchronization therapy (CRT) (2, 4) is an important example of such a treatment. Twenty to forty percent of patients with heart failure have an abnormal electrical activation sequence (e.g., left bundle branch block), which causes dyssynchronous contraction of muscles in different parts of the ventricle. Dyssynchronous contraction, in turn, causes a reduction in LV pump function by up to 20% beyond that which exists as a consequence of intrinsic muscle dysfunction and chamber dilation (14, 52). This is because in the presence of dyssynchrony, the mass of muscle that is activated early contracts against neighboring muscle in a weak (preexcited) state; the early activated muscle shortens at the expense of lengthening of the neighboring muscle, which reduces force generation, thus reducing pressure generation (14, 24). CRT is a treatment in which the heart is simultaneously paced from one right ventricular endocardial site and one LV epicardial site; access to the LV epicardial site is achieved minimally invasively by a pacing lead inserted via the coronary sinus to a distal coronary vein, thus simultaneously activating the would-be early- and late-activated regions. When electrically synchronized in this manner, mechanical synchrony is improved, and there is an immediate increase in ventricular contractility (52). This increase in chamber pump strength is achieved with no significant increase in myocardial oxygen consumption for the amount of work performed, as detailed previously (14, 52). In brief, it has been proposed that a conduction defect reduces the effective mass of muscle contributing to pressure generation, although the ineffective mass still consumes oxygen at a rate equivalent to that consumed in a mechanically unloaded state by basal metabolism and due to calcium cycling. Thus a dyscoordinated contraction leads to a metabolically inefficient state. With restoration of synchrony, the previously ineffective muscle mass is now contributing to contraction with a relatively small increase in oxygen consumption due only to the added amount of work being performed (i.e., there is no increase in oxygen consumed for basal metabolism or calcium cycling).

The Multicenter InSync Randomized Clinical Evaluation trial (2) showed that compared with a placebo treatment in patients with New York Heart Association (NYHA) class III or IV symptoms, ejection fraction  $\leq 35\%$ , and a QRS duration  $\geq 130$ ms, CRT more frequently reduced NYHA class and

Address for reprint requests and other correspondence: D. Burkhoff, Div. of Cardiology, Columbia Univ., Black Bldg. 812, 650 W. 168th St., New York, NY 10032 (E-mail: db59@columbia.edu).

improved quality of life (measured by the Minnesota Living with Heart Failure Questionnaire) and exercise tolerance (measured by both the 6-min hall walk and by peak oxygen consumption measured during cardiopulmonary stress testing). More recently, the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure trial (12) showed in a similar patient population (NYHA class III or IV, ejection fraction  $\leq 35\%$ , QRS  $\geq 120$  ms, and a hospitalization for heart failure within 12 mo before enrollment) that this treatment reduces the combined risk of death from any cause or first hospitalization (12). Accordingly, CRT is approved by the United States Food and Drug Administration for NYHA class III and IV chronic heart failure patients with ejection fraction  $\leq 35\%$  and QRS duration  $\geq 120$  ms. With multiple studies showing that implanted cardiac defibrillators (ICD) improve survival in the same group of patients for which CRT is indicated (12), a majority of devices being implanted incorporate both CRT and ICD functions.

One limitation of CRT is that it has only been shown to be effective in patients with prolonged QRS duration, which account for less than half of patients with class III or IV symptoms. In fact, one study (5) showed significant improvements in patients with QRS durations  $\geq 150$  ms, whereas fewer improvements were seen with QRS durations between 120 and 150 ms. Availability of a treatment that would be as easily deployable as CRT and as effective in patients with normal QRS duration could have a substantial impact on heart failure treatment. Further consideration of the pathophysiological mechanisms underlying contractile dysfunction in heart failure provided additional clues for the development of new approaches.

#### BRIEF OVERVIEW OF EXCITATION-CONTRACTION COUPLING AND DEFECTS IN HEART FAILURE

In cardiac muscle, calcium enters the cell during the plateau of the action potential through voltage-sensitive L-type calcium channels. This initial rise in intracellular calcium concentration ( $[Ca^{2+}]_i$ ) induces the release of larger amounts of calcium from the sarcoplasmic reticulum (SR; calcium-induced calcium release) and itself mostly enters the SR to become available for release on subsequent excitations. Calcium is removed from the cytosol by SR ATP-dependent calcium pumps and by the sarcolemmal sodium/calcium exchanger (8).

One cellular defect that underlies myocardial contractile dysfunction in heart failure of all causes is a reduction in the peak and broadening of the time course of the intracellular calcium transient (33), which leads to systolic and diastolic contractile abnormalities. Except for cases of rare genetic abnormalities, these changes in calcium cycling are not primary causes of heart failure but reflect secondary changes in both expression of genes encoding calcium handling proteins (29) and posttranslational modification of these proteins, many of which result from the abnormalities of  $\beta$ -adrenergic signaling. Several of the commonly discussed abnormalities include downregulation of genes encoding for the sarco(endo)plasmic reticular ATPase-dependent calcium pump [sarco(endo)plasmic reticulum  $Ca^{2+}$ -ATPase 2a (SERCA2a)] (32, 38, 48, 53), changes in expression and hypophosphorylation of phospholamban (31, 37, 48, 53, 71, 72), altered regulation of the sodium/calcium exchanger (39, 53, 74), and hyperphosphory-

lation of the ryanodine release channel (41, 45, 75). Although there are still controversies surrounding many aspects of these observations, there is general agreement that important changes in the regulation of the calcium transient occur in chronic heart failure and that these appear to result from the chronic neurohormonal stimulation present in heart failure discussed above. Indeed, some of the abnormalities noted are reversed during chronic  $\beta$ -blocker therapy (69). Accordingly, treatments aimed at improving the calcium transient in heart failure could be therapeutic (25).

Early studies of isolated cardiac muscle showed that use of voltage-clamp techniques to modulate the amplitude and duration of the action potential could modulate calcium entry and contractility in isolated papillary muscles (76). Increases in the duration of depolarization or the voltage during depolarization have each been associated with increases in the strength of cardiac muscle contraction. A relationship between action potential characteristics and calcium transients has been confirmed in myocardium from a rapid pacing heart failure model in dogs (53). However, because voltage clamping is not applicable to the intact heart, this type of approach was never thought of as a potential therapy for patients with heart failure. A conceptual breakthrough occurred with the recognition that similar effects could be achieved with extracellular field stimulation of myocardial tissue.

#### EXTRACELLULAR ELECTRIC SIGNALS CAN MODIFY THE STRENGTH OF CARDIAC CONTRACTION

Initial demonstration of this concept was obtained when square-wave current pulses were applied during the absolute refractory period in isolated, superfused, isometrically contracting rabbit papillary muscles. In this preparation, these signals were shown to significantly influence isometric contractile strength (Fig. 1A). Signals of negative amplitude (cathodic currents) were shown to reduce force, whereas positive amplitude (anodic currents) increased force. In either case, force of contraction was modified within one beat after introduction of signal application and reached a new steady-state level after approximately six to eight beats. The sequence was reversed after cessation of the signal. These signals have been referred to as cardiac contractility modulation (CCM) signals. CCM signals are referred to as nonexcitatory, because they are delivered during the refractory period and therefore do not elicit a new action potential.

In general, CCM signals are characterized by several parameters (Fig. 2). First is the time delay from the onset of local electrical activation at which they are delivered. Next is whether they are monophasic or biphasic. The amplitude is then specified (peak to peak) and can be expressed in terms of either current or voltage. The duration of each phase is specified in milliseconds. The final characteristic is the number of pulses delivered during each refractory period.

Borrowing from earlier literature about how changes in action potential characteristics may influence contractility, several studies were undertaken to investigate possible mechanisms of the effects of CCM signals. First, transmembrane action potential recordings taken during CCM signal application showed CCM duration-dependent increases in the duration and amplitude of the action potential (15). It was hypothesized that such changes in the action potential configuration provide

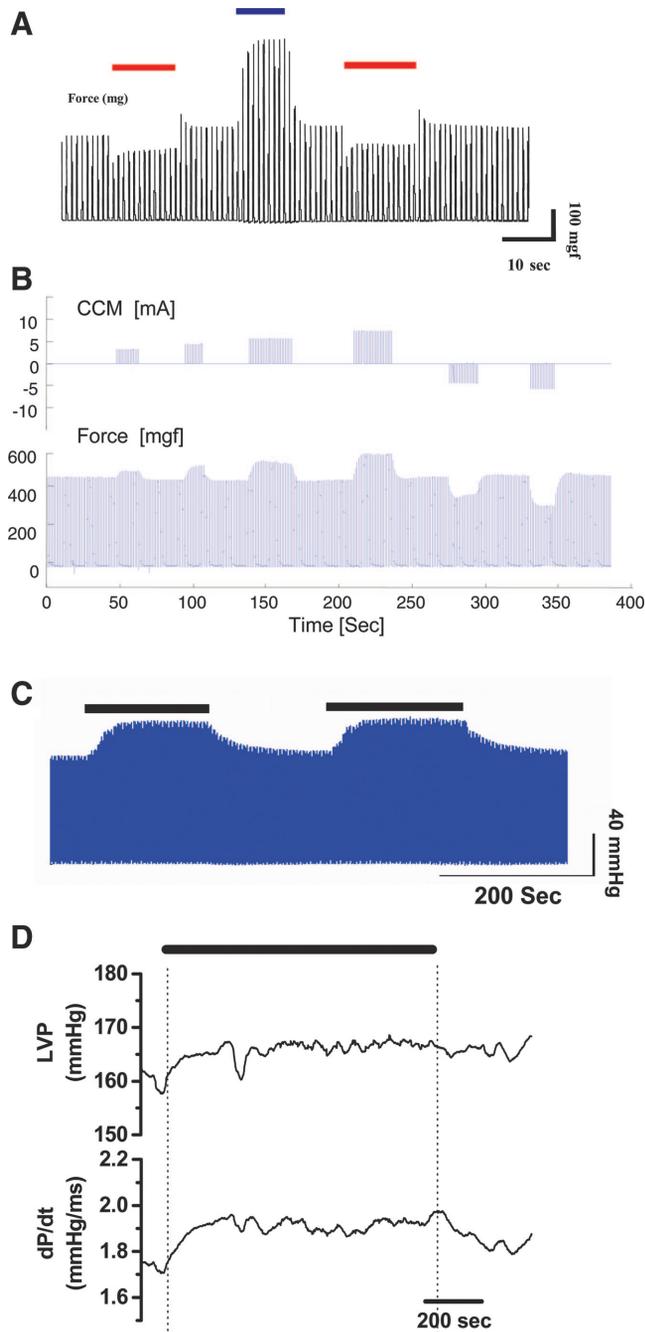


Fig. 1. Impact of cardiac contractility modulation (CCM) signals on isometric force generation in normal rabbit papillary muscle (A; red bars show times of anodic current delivery; blue bar shows time of cathodic current delivery), isometric force generation in human myocardium with end-stage heart failure (B; top trace shows CCM current amplitude and bottom trace shows force), left ventricular (LV) pressure (LVP) during CCM application (C; bars show times of CCM signal application), and peak LVP and peak maximal first derivative of LVP ( $dP/dt_{max}$ ) measured from a patient during acute CCM delivery (D; bar shows times of CCM signal application).

the electromotive force to enhance transsarcolemmal calcium flux. This hypothesis was confirmed in studies of isovolumically contracting Langendorff-perfused ferret hearts loaded with aequorin (50). The results showed that CCM signals increased peak  $[Ca^{2+}]_i$  as the proximate mechanism of inotropy in the acute setting. Finally, it was shown that the SR plays a central role in mediation of the inotropic effect (13).

As noted above, SR function is believed to be blunted in heart failure, raising the possibility that the CCM signal may not be as effective in improving contractile force in that setting. Trabeculae obtained from human hearts explanted from patients with severe heart failure at the time of cardiac transplantation were therefore studied in a similar manner as the rabbit papillary muscles described above (15). It was shown in these studies that CCM signals enhanced cardiac contractility in this preparation as well (Fig. 1B). On average, the CCM signal increased developed force by an average of ~30% from its baseline value compared with that observed in normal rabbit myocardium with CCM signals having the same parameters. This finding may be compatible with recent studies of end-stage failing human myocardium showing that, although there is markedly downregulated SERCA2a expression (Northern blot analysis), the ability of SR vesicles to accumulate calcium is impaired by only about 25% (39). This degree of functional impairment is believed to be sufficient to result in the inability of the failing heart to increase contractile strength with increases in heart rate, i.e., the failing heart lacks a normal, positive force-frequency relationship (38). On the other hand, the degree of retained SR function appears sufficient to permit existence of the CCM effect.

CCM EFFECTS IN INTACT HEARTS

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 in the field (e.g., nerves, skeletal muscles, etc.). It was next tested whether contractile strength of an entire heart could be enhanced by CCM application to a region of the hearts of anesthetized dogs. Studies were performed in different laboratories in normal animals (49) and in animals in which heart failure had been introduced by repeated coronary artery micro-embolizations (51, 70). These studies showed that there was a repeatable significant effect on pressure generation [Fig. 1C (51)], maximum first derivative of LV pressure ( $dP/dt_{max}$ ), ejection fraction, and end-systolic pressure-volume relationship (ESPVR), all indicative of an increase in ventricular

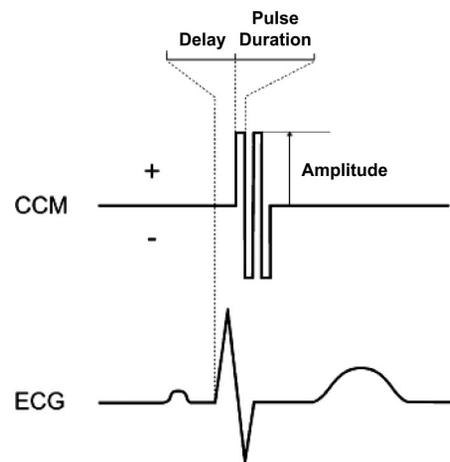


Fig. 2. CCM signals being investigated currently typically consist of two biphasic square-wave pulses having an amplitude of  $\pm 5-8$  V with a total duration ~20 ms, delivered ~30 ms after the detection of local myocardial activation during the absolute refractory period.

contractility that dissipated when the CCM signal delivery was ceased.

One set of studies explored the effects of CCM signals on the ventricular ESPVR. Ventricular volume was measured using ultrasonic crystals placed at multiple sites on the heart; volumes were estimated from continuously tracked ventricular dimensions and assuming an ellipsoidal ventricular geometry (49). These studies showed the upward shift of the ESPVR indicative of the increase in global ventricular contractile strength. In these same experiments, regional myocardial function was assessed using these same crystals by constructing regional pressure-segment length loops. The results showed that contractile performance was enhanced only in the region near the site of stimulation, and there was an accompanying reduction in regional end-diastolic segment length. Remotely, there were subtle changes in the shape of the pressure-length segment loop but no effect on contractility. It was further shown that when CCM signals are delivered to two sites, the effects on global function were additive.

Interestingly, when applied acutely to hearts of dogs with chronic heart failure, CCM treatment has also been shown to be associated with no significant change in global myocardial oxygen consumption (70). This may reflect the fact that offsetting factors influencing metabolic demand are in effect. On the one hand, there is an increase in regional contractility, which would be expected to increase regional oxygen consumption, whereas on the other hand, there is a local reduction in end-diastolic segment length, which would tend to reduce regional oxygen consumption. Alternatively, it may be difficult to detect regional changes in myocardial oxygen consumption, particularly from the septal wall, for which a significant proportion of venous blood may drain directly into the right ventricle and not appear in the coronary sinus. Finally, therapies that switch metabolism from free fatty acid utilization to glucose utilization have also been associated with enhanced function without increased oxygen consumption (6, 16, 17, 23). Whether or not CCM signals influence metabolism in this manner is not known.

#### INITIAL CLINICAL STUDY OF CCM SIGNALS

The initial tests of the acute effects of CCM signals performed in isolated papillary muscles and intact hearts of larger animals noted above set the stage for studies in human subjects with heart failure. The initial study involved short-term (10–30 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 ICD implantation or an electrophysiology study for evaluation of ventricular or supraventricular arrhythmias) (62–64). The findings showed the feasibility of delivering CCM treatment in humans and demonstrated that contractile performance could be enhanced (Fig. 1D). The signals were applied to patients with normal and prolonged QRS complexes, and similar acute effects were identified in both groups. In the patients with long QRS, CCM signals were also applied in addition to CRT; the effects on acute contractile performance as quantified by  $dP/dt_{max}$  of CRT and CCM were shown to be additive. Similar to the effects in dogs with heart failure, this increase in contractile performance was not associated with detectable changes in global myocardial oxygen consumption. The first chronic ap-

plication of CCM signals in heart failure patients was performed in a small group of patients who enrolled into two multicenter studies designed mainly to test the functionality of an implantable device that automatically delivers CCM signals (the OPTIMIZER System) (61, 73). Although improvements in patient symptoms, ejection fraction, quality of life, and exercise were reported, these findings must be taken within the context that they derived from unblinded, uncontrolled, treatment-only studies in a small number of patients. Nevertheless, no overt safety concerns were revealed from these studies. Two multicenter, randomized, controlled studies of CCM are currently underway (one in Europe and one in the United States being performed under an investigational device exemption from the United States Food and Drug Administration) to definitively test the safety and efficacy of CCM as a treatment for heart failure.

#### FUTURE RESEARCH

Although a significant amount of work has been done over the past several years to investigate the mechanisms and effects of CCM, many questions remain. The basic studies noted above have explored only acute CCM signal applications, and only recently are new data becoming available on longer term effects. 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 (22, 28)] and improved expression and phosphorylation of the sodium/calcium exchanger, phospholamban, and connexin43 (34–36, 46, 47, 68). Ongoing studies are aimed at further clarification of these and other effects of CCM when applied chronically in the setting of heart failure. As noted above, two clinical studies are underway to definitively test the safety and efficacy of CCM in patients with normal QRS durations who have NYHA class III or IV symptoms despite optimal medical therapy.

In summary, despite marked advances in pharmacotherapy, a growing number of patient have advanced heart failure with poor exercise tolerance and quality of life. With recognition that we may have reached a point where further blockade of the neurohormonal pathways responsible in large part for ventricular remodeling may not be possible, some investigators are beginning to refocus attention on means of directly improving pump function. Indeed, in a recent editorial, Dorn and Molteni recently wrote (25) that “There is a strong and obvious rationale for inotropic therapy in heart failure. At the whole-organ level, the hallmark of dilated cardiomyopathy is diminished systolic ventricular function. At the cellular level, most studies have shown diminished cardiomyocyte contractility in heart failure. Indeed, at the biochemical level, abnormalities of  $\beta$ -adrenergic receptor signaling and SR calcium cycling appear to be the critical lesions. Clearly, then, therapy should be targeted at increasing cardiomyocyte and ventricular contractility by augmenting the  $\beta$ -adrenergic/SERCA axis.” Additionally, prior adverse experiences with  $\beta$ -agonists and phosphodiesterase inhibitors should not be extrapolated to all forms of treatment aimed at enhancing ventricular contractility. Experience with CRT indicates that such approaches can be safe and effective treatments for heart failure.

Although current studies are not definitive and the mechanisms of action in both acute and chronic settings require further elucidation, nonexcitatory CCM signals also appear to influence myocardial contraction via mechanisms different than  $\beta$ -agonists and phosphodiesterase inhibitors. Also, being a site-specific device-based treatment, CCM lacks the peripheral effects of pharmacological agents and, as a further differentiating feature, can be turned on and off as desired. Clinical studies to define the risks associated with this form of treatment and the nature and magnitude of potential benefits are underway.

## DISCLOSURES

D. Burkhoff is an employee and S. A. Ben Haim is cochairman of IMPULSE Dynamics, Incorporated, the developer of CCM treatment for heart failure.

## REFERENCES

2. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, and Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 346: 1845–1853, 2002.
3. Adams KF Jr. New epidemiologic perspectives concerning mild-to-moderate heart failure. *Am J Med* 110, Suppl 7A: 6S–13S, 2001.
4. Auricchio A and Abraham WT. Cardiac resynchronization therapy: current state of the art: cost versus benefit. *Circulation* 109: 300–307, 2004.
5. Auricchio A, Stellbrink C, Butter C, Sack S, Vogt J, Misier AR, Bocker D, Block M, Kirkels JH, Kramer A, and Huvelle E. Clinical efficacy of cardiac resynchronization therapy using left ventricular pacing in heart failure patients stratified by severity of ventricular conduction delay. *J Am Coll Cardiol* 42: 2109–2116, 2003.
6. Bagger JP, Botker HE, Thomassen A, and Nielsen TT. Effects of ranolazine on ischemic threshold, coronary sinus blood flow, and myocardial metabolism in coronary artery disease. *Cardiovasc Drugs Ther* 11: 479–484, 1997.
7. Barbone A, Holmes JW, Heerdt PM, The' AH, Naka Y, Joshi N, Daines M, Marks AR, Oz MC, and Burkhoff D. Comparison of right and left ventricular responses to left ventricular assist device support in patients with severe heart failure: a primary role of mechanical unloading underlying reverse remodeling. *Circulation* 104: 670–675, 2001.
8. Bers DM. Cardiac excitation-contraction coupling. *Nature* 415: 198–205, 2002.
9. Braunwald E. Shattuck lecture—cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. *N Engl J Med* 337: 1360–1369, 1997.
10. Bristow MR.  $\beta$ -Adrenergic receptor blockade in chronic heart failure. *Circulation* 101: 558–569, 2000.
11. Bristow MR, Feldman AM, and Saxon LA. Heart failure management using implantable devices for ventricular resynchronization: Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial. COMPANION Steering Committee and COMPANION Clinical Investigators. *J Card Fail* 6: 276–285, 2000.
12. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, and Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 350: 2140–2150, 2004.
13. Brunckhorst C, Shemer I, Mika Y, Ben-Haim SA, and Burkhoff D. Cardiac contractility modulation by non-excitatory currents: studies in isolated cardiac muscle. *Eur J Heart Failure*. In press.
14. Burkhoff D, Oikawa RY, and Sagawa K. Influence of pacing site on canine left ventricular contraction. *Am J Physiol Heart Circ Physiol* 251: H428–H435, 1986.
15. Burkhoff D, Shemer I, Felzen B, Shimizu J, Mika Y, Dickstein M, Prutchi D, Darvish N, and Ben-Haim SA. Electric currents applied during the refractory period can modulate cardiac contractility in vitro and in vivo. *Heart Fail Rev* 6: 27–34, 2001.
16. Burkhoff D, Weiss RG, Schulman SP, Kalil-Filho R, Wannenburg T, and Gerstenblith G. Influence of metabolic substrate on rat heart function and metabolism at different coronary flows. *Am J Physiol Heart Circ Physiol* 261: H741–H750, 1991.
17. Chandler MP, Stanley WC, Morita H, Suzuki G, Roth BA, Blackburn B, Wolff A, and Sabbah HN. Short-term treatment with ranolazine improves mechanical efficiency in dogs with chronic heart failure. *Circ Res* 91: 278–280, 2002.
18. Chung ES, Packer M, Lo KH, Fasanmade AA, and Willerson JT. Randomized, double-blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor- $\alpha$ , in patients with moderate-to-severe heart failure: results of the anti-TNF Therapy Against Congestive Heart Failure (ATTACH) trial. *Circulation* 107: 3133–3140, 2003.
19. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong and M. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 325: 303–310, 1991.
20. Cohn JN, Pfeffer MA, Rouleau J, Sharpe N, Swedberg K, Straub M, Wiltse C, and Wright TJ. Adverse mortality effect of central sympathetic inhibition with sustained-release moxonidine in patients with heart failure (MOXCON). *Eur J Heart Fail* 5: 659–667, 2003.
21. Cohn JN and Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 345: 1667–1675, 2001.
22. Colucci WS. Molecular and cellular mechanisms of myocardial failure. *Am J Cardiol* 80: 15L–25L, 1997.
23. Conti CR. Partial fatty acid oxidation (pFOX) inhibition: a new therapy for chronic stable angina. *Clin Cardiol* 26: 161–162, 2003.
24. Curry CW, Nelson GS, Wyman BT, Declerck J, Talbot M, Berger RD, McVeigh ER, and Kass DA. Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging. *Circulation* 101: E2, 2000.
25. Dorn GW and Molkentin JD. Manipulating cardiac contractility in heart failure: data from mice and men. *Circulation* 109: 150–158, 2004.
26. Feldman AM, Baughman KL, and Strobeck JE. Oral milrinone in severe chronic heart failure. *N Engl J Med* 326: 1565–1566, 1992.
27. Feldman AM, Bristow MR, Parmley WW, Carson PE, Pepine CJ, Gilbert EM, Strobeck JE, Hendrix GH, Powers ER, and Bain RP. Effects of vesnarinone on morbidity and mortality in patients with heart failure. Vesnarinone Study Group. *N Engl J Med* 329: 149–155, 1993.
28. Feldman AM, Weinberg EO, Ray PE, and 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* 73: 184–192, 1993.
29. Fiedler B and Wollert KC. Interference of antihypertrophic molecules and signaling pathways with the  $\text{Ca}^{2+}$ -calcineurin-NFAT cascade in cardiac myocytes. *Cardiovasc Res* 63: 450–457, 2004.
30. Foody JM, Farrell MH, and Krumholz HM.  $\beta$ -Blocker therapy in heart failure: scientific review. *JAMA* 287: 883–889, 2002.
31. Frank K and Kranias EG. Phospholamban and cardiac contractility. *Ann Med* 32: 572–578, 2000.
32. Frank KF, Bolck B, Brixius K, Kranias EG, and Schwinger RH. Modulation of SERCA: implications for the failing human heart. *Basic Res Cardiol* 97, Suppl 1: I72–I78, 2002.
33. Gomez AM, Valdivia HH, Cheng H, Lederer MR, Santana LF, Cannell MB, McCune SA, Altschuld RA, and Lederer WJ. Defective excitation-contraction coupling in experimental heart failure. *Science* 276: 800–806, 1997.
34. Gupta RC, Mishra S, Rastogi S, Imai M, Hadad W, Mika Y, and Sabbah HN. 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 (Abstract). *Eur Heart J* 25: 1116, 2004.
35. Gupta RC, Mishra S, Rastogi S, Imai M, Haddad W, Mika Y, and Sabbah HN. Short-term therapy with non-excitatory modulation electric signals increases phosphorylation of phospholamban in left ventricular myocardium of dogs with chronic heart failure (Abstract). *Eur Heart J* 25: 1116, 2004.
36. Gupta RC, Mishra S, Sharad R, Imai M, Haddad W, Mika Y, and Sabbah HN. 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 (Abstract). *J Am Coll Cardiol*. In press.
37. **Haghighi K, Gregory KN, and Kranias EG.** Sarcoplasmic reticulum Ca-ATPase-phospholamban interactions and dilated cardiomyopathy. *Biochem Biophys Res Commun* 322: 1214–1222, 2004.
  38. **Hasenfuss G, Reinecke H, Studer R, Meyer M, Pieske B, Holtz J, Holubarsch Ch, Posival H, Just H, and Drexler H.** Relation between myocardial function and expression of sarcoplasmic reticulum  $Ca^{2+}$ -ATPase in failing and nonfailing human myocardium. *Circ Res* 75: 434–442, 1994.
  39. **Heerdt PM, Holmes JW, Cai B, Barbone A, Madigan JD, Reiken S, Lee DL, Oz MC, Marks AR, and Burkhoff D.** Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. *Circulation* 102: 2713–2719, 2000.
  40. **Klotz S, Barbone A, Reiken S, Holmes JW, Naka Y, Oz MC, Marks AR, and Burkhoff D.** Left ventricular assist device support normalizes left and right ventricular  $\beta$ -adrenergic pathway properties. *J Am Coll Cardiol*. In press.
  41. **Li Y, Kranias EG, Mignery GA, and Bers DM.** Protein kinase A phosphorylation of the ryanodine receptor does not affect calcium sparks in mouse ventricular myocytes. *Circ Res* 90: 309–316, 2002.
  42. **Mann DL.** Inflammatory mediators and the failing heart: past, present, and the foreseeable future. *Circ Res* 91: 988–998, 2002.
  43. **Mann DL.** Stress-activated cytokines and the heart: from adaptation to maladaptation. *Annu Rev Physiol* 65: 81–101, 2003.
  44. **Mann DL, McMurray JJ, Packer M, Swedberg K, Borer JS, Colucci WS, Djian J, Drexler H, Feldman A, Kober L, Krum H, Liu P, Nieminen M, Tavazzi L, Van Veldhuisen DJ, Waldenstrom A, Warren M, Westheim A, Zannad F, and Fleming T.** Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). *Circulation* 109: 1594–1602, 2004.
  45. **Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, Rosembli N, and Marks AR.** PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell* 101: 365–376, 2000.
  - 45a. **Metoprolol CR/XL Randomized Intervention Trial.** Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 353: 2001–2007, 1999.
  46. **Mishra S, Gupta RC, Haddad W, Rastogi S, Imai M, Mika Y, and Sabbah HN.** 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 (Abstract). *J Card Fail* 10: 153, 2004.
  47. **Mishra S, Gupta RC, Rastogi S, Haddad W, Mika Y, and 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 (Abstract). *Circulation* 110: III-604, 2004.
  48. **Mishra S, Gupta RC, Tiwari N, Sharov VG, and Sabbah HN.** Molecular mechanisms of reduced sarcoplasmic reticulum  $Ca^{2+}$  uptake in human failing left ventricular myocardium. *J Heart Lung Transplant* 21: 366–373, 2002.
  49. **Mohri S, He KL, Dickstein M, Mika Y, Shimizu J, Shemer I, Yi GH, Wang J, Ben-Haim S, and Burkhoff D.** Cardiac contractility modulation by electric currents applied during the refractory period. *Am J Physiol Heart Circ Physiol* 282: H1642–H1647, 2002.
  50. **Mohri S, Shimizu J, Mika Y, Shemer I, Wang J, Ben-Haim S, and Burkhoff D.** Electric currents applied during the refractory period enhance contractility and systolic calcium in the ferret heart. *Am J Physiol Heart Circ Physiol* 284: H1119–H1123, 2003.
  51. **Morita H, Suzuki G, Haddad W, Mika Y, Tanhecho EJ, Sharov VG, Goldstein S, Ben-Haim S, and Sabbah HN.** Cardiac contractility modulation with nonexcitatory electric signals improves left ventricular function in dogs with chronic heart failure. *J Card Fail* 9: 69–75, 2003.
  52. **Nelson GS, Berger RD, Fetis BJ, Talbot M, Hare JM, Kass DA, and Spinelli JC.** Left ventricular or biventricular pacing improves cardiac function at diminished energy cost in patients with dilated cardiomyopathy and left bundle-branch block. *Circulation* 102: 3053–3059, 2000.
  53. **O'Rourke B, Kass DA, Tomaselli GF, Kaab S, Tunin R, and Marban E.** Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. *Circ Res* 84: 562–570, 1999.
  54. **Packer M.** Neurohormonal interactions and adaptations in congestive heart failure. *Circulation* 77: 721–730, 1988.
  55. **Packer M.** Effect of phosphodiesterase inhibitors on survival of patients with chronic congestive heart failure. *Am J Cardiol* 63: 41A–45A, 1989.
  56. **Packer M.** Role of the sympathetic nervous system in chronic heart failure: a historical and philosophical perspective. *Circulation* 82, Suppl I: I1–I6, 1990.
  57. **Packer M.** The development of positive inotropic agents for chronic heart failure: how have we gone astray? *J Am Coll Cardiol* 22: 119A–126A, 2000.
  58. **Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, and Shusterman NH.** The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U S Carvedilol Heart Failure Study Group. *N Engl J Med* 334: 1349–1355, 1996.
  59. **Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, and Kukin ML.** Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 325: 1468–1475, 1991.
  60. **Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacs P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, and DeMets DL.** Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 344: 1651–1658, 2001.
  61. **Pappone C, Augello G, Rosanio S, Vicedomini G, Santinelli V, Romano M, Agricola E, Maggi F, Buchmayr G, Moretti G, Mika Y, Ben-Haim SA, Wolz M, Stix G, and Schmidinger H.** 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* 15: 418–427, 2004.
  62. **Pappone C, Rosanio S, Burkhoff D, Mika Y, Vicedomini G, Augello G, Shemer I, Prutchi D, Haddad W, Aviv R, Snir Y, Kronzon I, Alfieri O, and Ben-Haim SA.** 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* 90: 1307–1313, 2002.
  63. **Pappone C, Vicedomini G, Loricchio ML, Meloni C, Salvati A, Kimchy Y, Hadad W, Aviv R, Mika Y, Darvish N, Kronzon I, and Ben-Haim SA.** First clinical experience demonstrating improvement of hemodynamic parameters in heart failure patients through the application of non-excitatory electrical signals (Abstract). *J Am Coll Cardiol* 35, Suppl A: A-229, 2000.
  64. **Pappone C, Vicedomini G, Salvati A, Meloni C, Haddad W, Aviv R, Mika Y, Darvish N, Kimchy Y, Shemer I, Snir Y, Prutchi D, Ben-Haim SA, and Kronzon I.** Electrical modulation of cardiac contractility: clinical aspects in congestive heart failure. *Heart Fail Rev* 6: 55–60, 2001.
  65. **Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, Yusuf S, and Pocock S.** Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 362: 759–766, 2003.
  66. **Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, and Gatlin M.** Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 348: 1309–1321, 2003.
  67. **Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Palensky J, and Wittes J.** The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 341: 709–717, 1999.
  68. **Rastogi S, Mishra S, Habib O, Imai M, Gupta RC, Haddad W, Mika Y, Stanley WC, and Sabbah HN.** Therapy with non-excitatory cardiac contractility modulation electric signals reverses the maladaptive fetal gene program in LV myocardium of dogs with heart failure (Abstract). *Circulation* 108: IV-444, 2003.
  69. **Reiken S, Wehrens XH, Vest JA, Barbone A, Klotz S, Mancini D, Burkhoff D, and Marks AR.** Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. *Circulation* 107: 2459–2466, 2003.
  70. **Sabbah HN, Imai M, Haddad W, Habib O, Stanley WC, Chandler MP, and Mika Y.** Non-excitatory cardiac contractility modulation electric signals improve left ventricular function in dogs with heart failure without increasing myocardial oxygen consumption (Abstract). *Heart Rhythm* 1: S181, 2004.

71. Schmidt U, Hajjar RJ, Kim CS, Lebeche D, Doye AA, and Gwathmey JK. Human heart failure: cAMP stimulation of SR  $\text{Ca}^{2+}$ -ATPase activity and phosphorylation level of phospholamban. *Am J Physiol Heart Circ Physiol* 277: H474–H480, 1999.
72. Schwinger RH, Munch G, Bolck B, Karczewski P, Krause EG, and Erdmann E. Reduced  $\text{Ca}^{2+}$ -sensitivity of SERCA 2a in failing human myocardium due to reduced serine-16 phospholamban phosphorylation. *J Mol Cell Cardiol* 31: 479–491, 1999.
73. Stix G, Borggrefe M, Wolpert C, Hindricks G, Kottkamp H, Bocker D, Wichter T, Mika Y, Ben-Haim S, Burkhoff D, Wolzt M, and Schmidinger H. Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure. *Eur Heart J* 25: 650–655, 2004.
74. Studer R, Reinecke H, Bilger J, Eschenhagen T, Bohm M, Hasenfuss G, Just H, Holtz J, and Drexler H. Gene expression of the cardiac  $\text{Na}^{+}$ - $\text{Ca}^{2+}$  exchanger in end-stage human heart failure. *Circ Res* 75: 443–453, 1994.
75. Wehrens XH, Lehnart SE, and Marks AR. Intracellular calcium release channels and cardiac disease. *Annu Rev Physiol* Jul 21, 2004; Epub ahead of print.
76. Wood EH, Heppner RL, and 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* 24: 409–445, 1969.

Daniel Burkhoff\*†  
 Shlomo A. Ben-Haim‡  
 \*Division of Cardiology, Columbia University Medical School, New York; †IMPULSE Dynamics, Orangeburg, New York; and ‡Department of Biophysics, School of Medicine, Technion Israel Institute of Technology, Haifa, Israel

