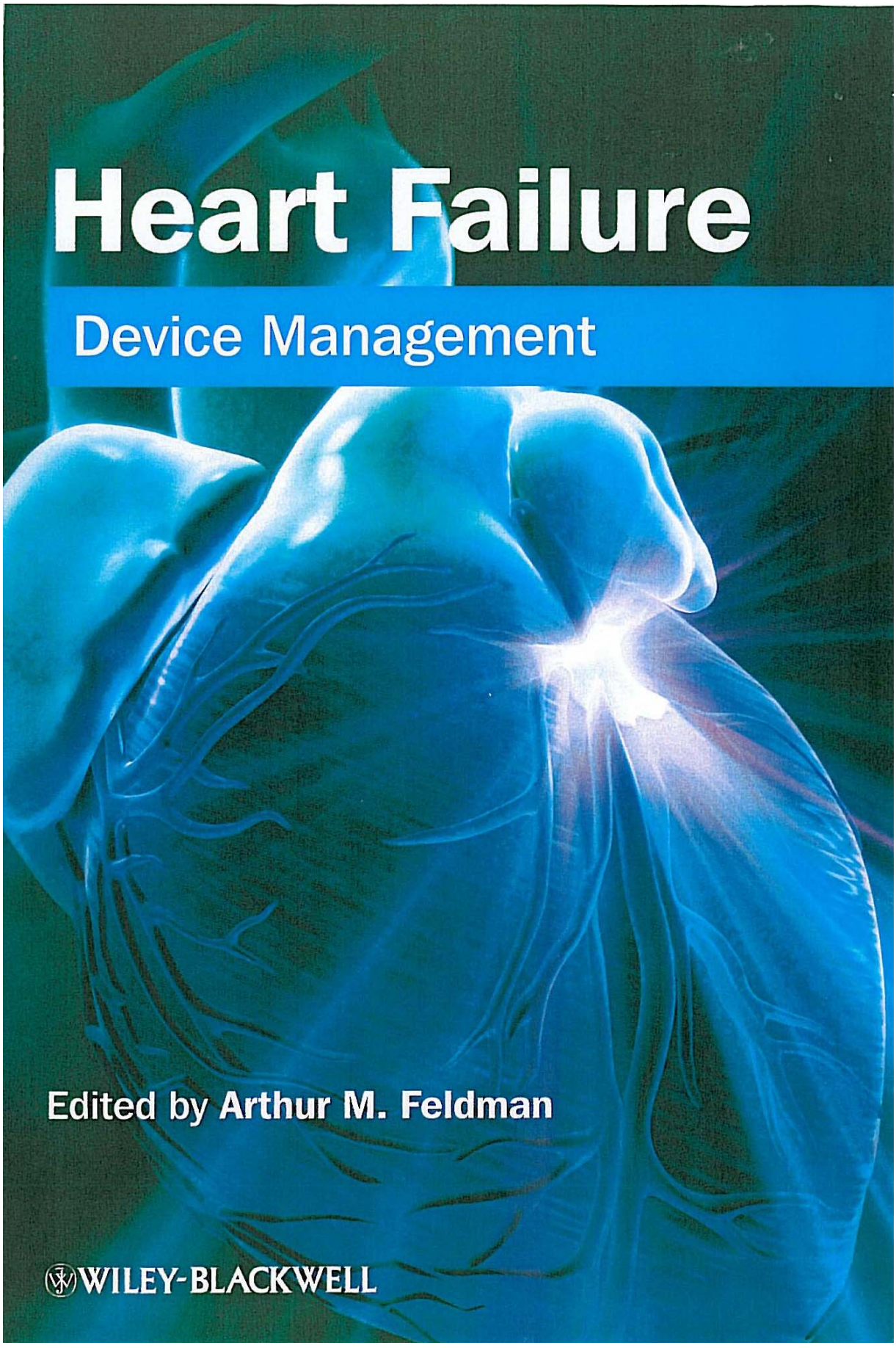
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Contents

CHAPTER 4

Cardiac Contractility Modulation by Electrical Signals Applied during the Absolute Refractory Period as a Treatment for Chronic Heart Failure

Daniel Burkhoff[1,2], *Hani N. Sabbah*[3], *Christian Butter*[4], *Yuval Mika*[2], & *Martin Borggrefe*[5]

[1]Columbia University, New York, NY, USA
[2]IMPULSE Dynamics USA, Orangeburg, NY, USA
[3]Henry Ford Health System, Detroit, MI, USA
[4]Heart Center Brandenburg Bernau/Berlin, Bernau, Germany
[5]Fakultät für klinische, Medizin der Universität Heidelberg, Mannheim, Germany

Clinical studies have shown that cardiac resynchronization therapy (CRT) improves patient symptoms, quality of life, exercise tolerance and reduces hospitalizations in patients with advanced heart failure and prolonged electrical activation (i.e., increased QRS duration) [1,2]. The results of a recent study showed that patients with mechanical dyssynchrony by tissue Doppler imaging but a normal QRS duration did not benefit from CRT [3]. Thus, QRS duration remains paramount in patient selection for CRT. In view of the fact that greater than 70% of patients with heart failure have a normal QRS duration [4], development of a device-based treatment for such patients with persistent symptoms despite optimal medical therapy would have an important impact.

Cardiac contractility modulating (CCM) signals are nonexcitatory signals applied during the absolute refractory period that have been shown to enhance the strength of left ventricular (LV) contraction in studies carried out in animals and humans with heart failure. Since the signals impact cell function without any impact on activation sequence, the effects are independent of QRS duration and additive to those of CRT in patients with prolonged QRS. We review here the concept and available basic and clinical results concerning the evaluation of CCM as a treatment for heart failure. Reviews of early findings have appeared previously [5,6].

CCM concept and underlying mechanisms

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 [7]. Such abnormalities reflect heart failure-associated changes

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in expression of genes encoding calcium handling proteins and posttranslational modification of their associated proteins. Several of the commonly discussed abnormalities include downregulation of genes encoding for the sarcoplasmic reticular ATPase-dependent calcium pump (SERCA2a) [8–11], changes in expression and hypophosphorylation of phospholamban (PLB) [10–15], altered regulation of the sodium–calcium exchanger [11,16,17], and hyperphosphorylation of the ryanodine release channel [18–20]. Accordingly, it has been proposed that treatments aimed at improving the calcium transient in heart failure could be therapeutic [21].

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 [22–25]. 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, increased 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 (Figure 4.1) [26,27]. These so-called *CCM signals* contain ~100 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

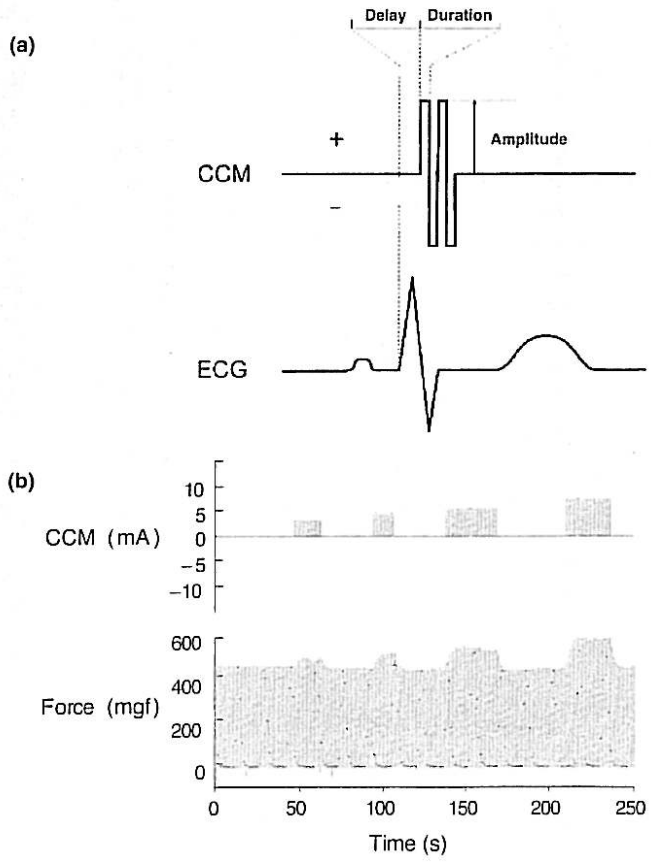

Figure 4.1 (a) Cardiac contractility modulating (CCM) signals employed in clinical study are biphasic pulses delivered after a defined delay from detection of local electrical activation. (b) Effects of CCM signals on isometric force measured from trabecular muscle of an end-stage failing heart obtained at heart transplant [27].

observed with paired pacing or post-extra systolic potentiation). CCM signals are thus referred to as nonexcitatory.

Borrowing from the earlier literature on voltage clamping [22–25], 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 entry, thus enhancing the strength of the heartbeat [26–28]. Whether this mechanism is in effect during intermediate (hours) or long-term (days and beyond) signal application is still not known, largely because methods to measure calcium transients in intact animals are not available.

Nevertheless, the next series of experiments were aimed at studies in large animal models, including animal models of heart failure. 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 and skeletal muscles). Studies were therefore 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 (Figure 4.2) [29]. 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

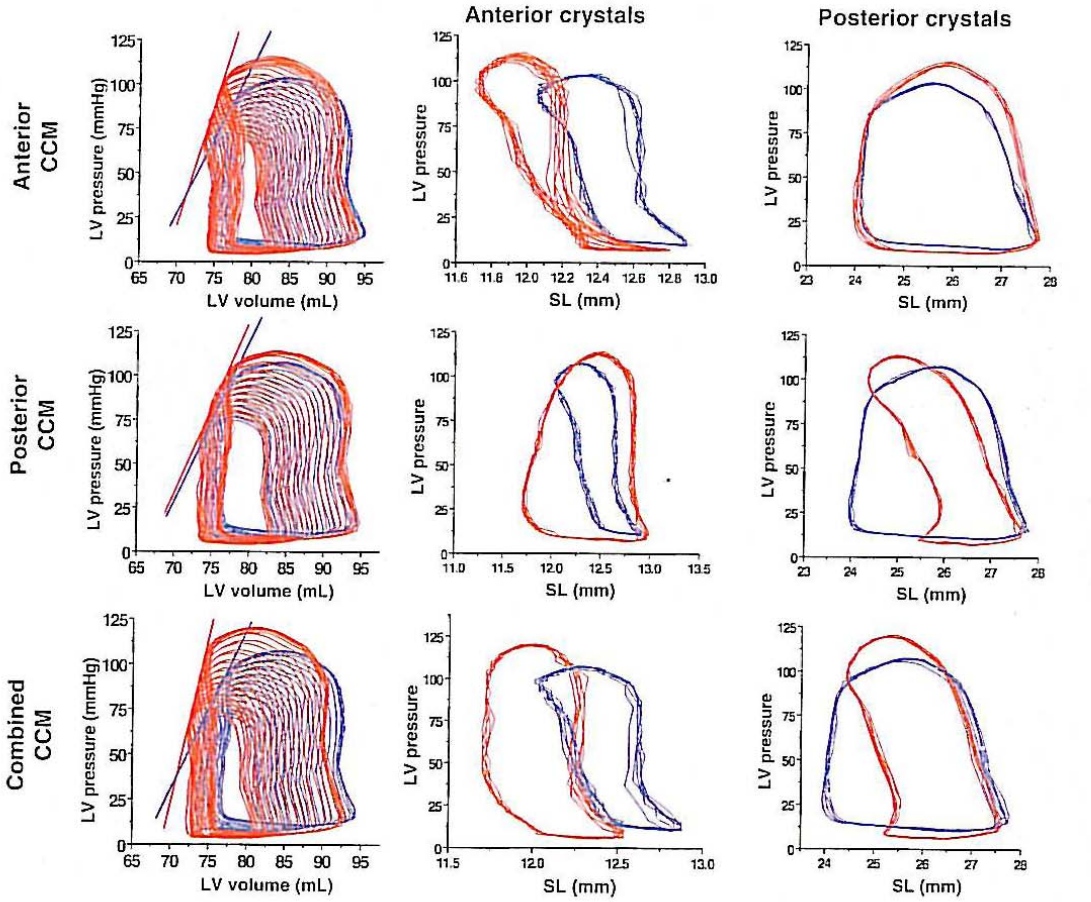

Figure 4.2 Effects of cardiac contractility modulating (CCM) signals on global function assessed by pressure–volume relations (first column) and on regional function in the anterior wall (second column) and posterior wall (third column) assessed by pressure-segment length loops when signals are applied to the anterior wall (first row), posterior wall (second row), and simultaneously to both walls (third row) [29]. Baseline shown in blue; measurements during CCM signal application shown in red. LV, left ventricular; SL, segment length. (Reproduced with permission from the American Physiological Society).

Table 4.1 Comparison between Sham-operated untreated and CCM-treated heart failure dogs for changes (Δ) between pre- and posttreatment (3-mo period) measurements.

	Sham group	*CCM-treated group*	p *value*
ΔHeart rate (beats/min)	12 ± 8	8 ± 4	NS
ΔSystolic aortic pressure (mmHg)	6 ± 6	1 ± 7	NS
ΔLV EDP (mmHg)	1 ± 2	−6 ± 2	0.029
ΔLV EDV (mL)	10 ± 1	−4 ± 2	0.0001
ΔLV ESV (mL)	11 ± 1	−7 ± 2	0.0001
ΔLV EF (%)	−4 ± 1	6 ± 1	0.0001
ΔStroke volume (mL)	−1 ± 0.5	3 ± 0.4	0.0001

CCM, cardiac contractility modulating signals; EDP, end-diastolic pressure; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LV, left ventricle; NS, nont significant.

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 important, these signals have been shown to have a similar effect in animals with heart failure. In one series of experiments, heart failure was induced by multiple sequential intracoronary microembolizations until ejection fraction (EF) was ≤40% [30,31]. Hemodynamic parameters and myocardial oxygen consumption were measured in an open chest, anesthetized state, with epicardial electrodes used to administer CCM signals. The results showed that while heart rate and peak LV pressure were not significantly influenced, acute CCM therapy decreased LV end-diastolic pressure and end-systolic volume. Consequently, LVEF and cardiac output increased significantly. The improvement in LV systolic function seen in this study was accompanied by unchanged total LV coronary blood flow and unchanged myocardial oxygen consumption.

To further explore the mechanisms underlying the chronic effects, dogs with heart failure induced by repeated coronary microembolization were implanted with a device to deliver CCM signals. Following implantation, dogs were randomized either to receive active CCM treatment for 5 h/day or for the device to remain off; both groups were followed for 3 months. At the end of the follow-up period, CCM-treated dogs had a significantly lower LV end-diastolic pressure, end-diastolic volume, and end-systolic volume, and significantly higher LV EF and stroke volume (Table 4.1). It should be emphasized that these hemodynamic measurements were made at a time when CCM signals were turned off. That means that the noted improvements in hemodynamic measurements reflect changes in intrinsic muscle properties, not just acute effects of CCM signals.

Therefore, in view of prior literature showing that electromagnetic fields can impact on protein–protein interaction and gene expression [26], we hypothesized that CCM signals may have a direct impact on cellular physiology beyond acute effects on calcium handling. To explore this hypothesis, myocardial samples were taken for molecular and biochemical analysis. Tissue samples were available from the animals from both the acute and chronic studies discussed above [32,33]; samples were also available from normal animals. In all cases, samples were taken from the interventricular septum (near the site of CCM signal delivery) and in a remote area on the LV free wall. Findings related to SERCA2a gene expression are illustrated by the Northern blots of Figure 4.3. For both acute and chronic experiments, glyceraldehyde 3-phosphate dehydrogenase (GAPDH) band intensities show relatively equal loading in each lane. Compared to normals, SERCA2a expression was decreased in all untreated heart failure animals in both the interventricular septum ("near") and remote from the LV free wall ("remote"). For tissue obtained from animals with acute (4 h) CCM treatment, SERCA2a expression increased in the region near the site of CCM signal administration, but not in the remote region. In the chronic setting, however, SERCA2a expression was improved in both near and remote

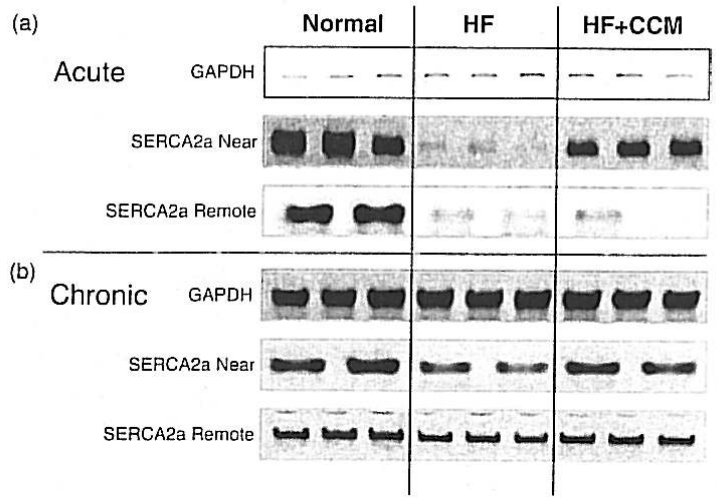

Figure 4.3 Northern blots showing impact of (a) acute (6 h) and (b) chronic (3 mo) cardiac contractility modulating (CCM) signal application on myocardial SERCA2a gene expression, both near and remote from the site of signal delivery. Tissue obtained from normal dogs, dogs with heart failure induced by repeated coronary microembolization, and similar heart failure dogs exposed to CCM treatment. As shown, acute CCM improve gene expression only in the region near where signals are delivered. However, in the chronic setting, gene expression is improved both near and remote from the site of signal delivery. (Reproduced with permission from [33]).

regions. These findings are representative of findings obtained with PLB. B-type natriuretic peptide (BNP) expression was also examined, but in this case, BNP was overexpressed in untreated heart failure, decreased acutely only in the region near the CCM pacing site, and decreased in both the near and remote sites with chronic CCM treatment. The fact that gene expression is improved in the short term only near the area of treatment implies that the effects of CCM treatment are local and direct. However, in the long run, where expression is improved in both near and remote sites, two possible factors may contribute. First, changes in gene expression in remote areas may be secondary to the global hemodynamic benefits provided by chronic regional CCM treatment. Alternatively, there may be some direct effect that is transmitted to remote sites via gap junctions. Which, if either, of these is contributory or dominant remains to be elucidated.

In the chronic study, mRNA expression of a larger array of genes was examined [33]. These included the housekeeping genes GAPDH and calsequestrin (CSQ), the fetal program genes consisting of β_1-adrenergic receptor (β_1-AR), α-myosin heavy chain (α-MHC), and A-type (ANP) and B-type (BNP) natriuretic peptides and the cardiac SR genes SERCA-2a, PLB, and RYR. Expression of GAPDH and CSQ was unchanged among the study groups (i.e., normal dogs, sham-operated heart failure dogs, and heart failure CCM-treated dogs). mRNA expression of β_1-AR, α-MHC, SERCA-2a, PLB, and RYR (ryanodine receptor) decreased and expression of ANP and BNP increased significantly in sham-operated heart failure dogs compared to normals. CCM therapy restored the expression of all genes to near-normal levels.

In addition to looking at mRNA expression, myocardial protein expression was examined in the myocardium from sites both near and remote from the site of CCM signal application. Protein levels of CSQ (a housekeeping gene product) were unchanged among the three study groups. Protein levels of β_1-AR, SERCA-2a, PLB, and RYR decreased and that of ANP and BNP increased significantly in sham-operated controls compared to normals. CCM therapy restored the expression of all measured proteins except for total PLB. The restoration of genes and proteins after 3 months of CCM therapy was the same in LV tissue obtained from

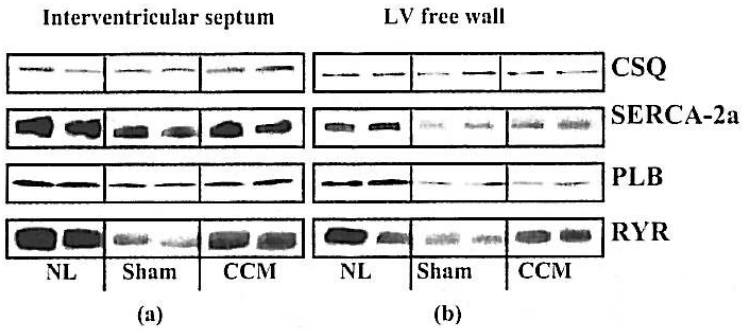

Figure 4.4 (a) Western blots of sarcoplasmic reticulum proteins in tissue obtained from the *interventricular septum* of 2 normal dogs (NL), 2 sham-operated heart failure dogs (Sham), and 2 cardiac contractility modulation (CCM) treated dogs [33]. (b) Western blots of the same proteins in tissue obtained from the *left ventricular (LV) free wall* of the same dogs as in (a) [33]. CSQ, calsequestrin; PLB, phospholamban; RYR, ryanodine receptor; SERCA-2a, calcium ATPase. (Reproduced with permission from [33]).

the interventricular septum, the site nearest to the CCM signal delivery leads, and the LV free wall, a site remote from the CCM leads (Figure 4.4).

Although protein levels of total PLB did not change with CCM, levels of PLB that was phosphorylated (P-PLB) at serine-16 and threonine-17 in tissue obtained from both the interventricular septum and the LV free wall were significantly lower in sham-operated heart failure dogs compared to normal dogs and returned to near-normal levels after 3 months of CCM therapy (Figure 4.5, Table 4.2). In both the interventricular septum and LV free wall, the ratio of P-PLB at serine-16 to total PLB and the ratio of P-PLB at threnonine-17 were also significantly lower in sham-operated heart failure dogs compared to normal dogs. Thus, the long-term CCM therapy resulted in a significant increase of both ratios in both the interventricular septum and the LV free wall (Table 4.2).

In summary, in the chronic setting, CCM signals have hemodynamic effects that persist even when the signals are turned off, at least for short (hours) periods of time. The longevity of those effects is not yet established. CCM signals applied to myocardium of dogs with chronic heart failure have relatively rapid impact on gene expression, but only in the region where they are applied. In the chronic setting, however, improved gene expression is present both local to and remote from the region of signal delivery. These findings potentially imply both direct and indirect effects of the signals on gene expression. Furthermore, similar improvements are seen at the protein level. Interestingly, as was the case for PLB for which total

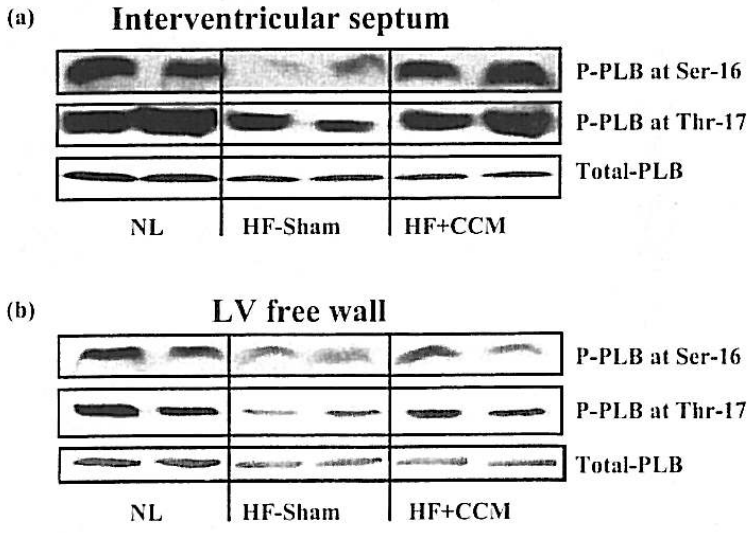

Figure 4.5 (a) Western blots of phospholamban (PLB) in tissue obtained from the interventricular septum of 2 normal dogs (NL), 2 sham-operated heart failure dogs (HF-Sham), and 2 cardiac contractility modulation treated heart failure dogs (HF + CCM). (b) Western blots of the same protein in tissue obtained from the left ventricular (LV) free wall of the same dogs as in (a). P-PLB at Ser-16, phosphorylated phospholamban at serine-16; P-PLB at Thr-17, phosphorylated phospholamban at threonine-17. (Reproduced with permission from [33]).

Table 4.2 Protein expression of total PLB and phosphorylated PLB at serine-16 and threonine-17 in the interventricular septum and left ventricle free wall of normal dogs (NL) ($n = 6$), Sham-operated untreated heart failure dogs (Sham; $n = 7$), and CCM-treated heart failure dogs (CCM; $n = 7$).

	Interventricular septum			*LV free wall*		
	NL	*Sham*	*CCM*	*NL*	*Sham*	*CCM*
Total PLB (du)	445 ± 7	305 ± 23*	299 ± 16*	446 ± 19	305 ± 19*	299 ± 9*
P-PLB Ser-16 (du)	85 ± 6	47 ± 5*	79 ± 6†	128 ± 11	50 ± 12*	87 ± 11*†
P-PLB Thr-17 (du)	146 ± 6	62 ± 10*	129 ± 12†	137 ± 4	56 ± 7*	109 ± 18†
P-PLB Ser-16/Total PLB	0.19 ± 0.01	0.15 ± 0.01*	0.27 ± 0.02†	0.29 ± 0.03	0.16 ± 0.03*	0.29 ± 0.04†
P-PLB Thr-17/Total PLB	0.33 ± 0.01	0.21 ± 0.04*	0.44 ± 0.05†	0.31 ± 0.02	0.19 ± 0.03*	0.36 ± 0.05†

* $p < 0.05$ vs NL.

† $p < 0.05$ vs Sham.

CCM, cardiac contractility modulating signals; du, densitometric units; PLB, phospholamban; P-PLB, phosphorylated phospholamban; Ser-16, serine-16; Thr-17, theonine-17.

protein expression was not changed significantly, the ratio of total-to-phosphorylated PLB improved in a manner that would result in improved SR calcium handling. Thus, the mechanisms by which CCM signal impact myocardial properties appear to go far beyond the original hypotheses related to acute augmentation of calcium handling.

Initial clinical study of acute CCM signals

The initial clinical study of CCM signals involved short-term (10–30 min) CCM signal application using a desktop signal generator and 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 a study for evaluation of ventricular or supraventricular arrhythmias) [34,35]. This study involved patients with an average (±SD) age of 60 ± 11 years with 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 (Figure 4.6). The data from all patients studied showed an average ~10% increase in dP/dt_{max}, which was independent of baseline QRS duration (Figure 4.6a). In a subgroup of the patients with long QRS, CCM signals were also applied simultaneously with biventricular pacing (which is equivalent to CRT); the effects on acute contractile performance as quantified by dP/dt_{max} of CRT and CCM were shown to be additive in most patients (Figure 4.6b) [34].

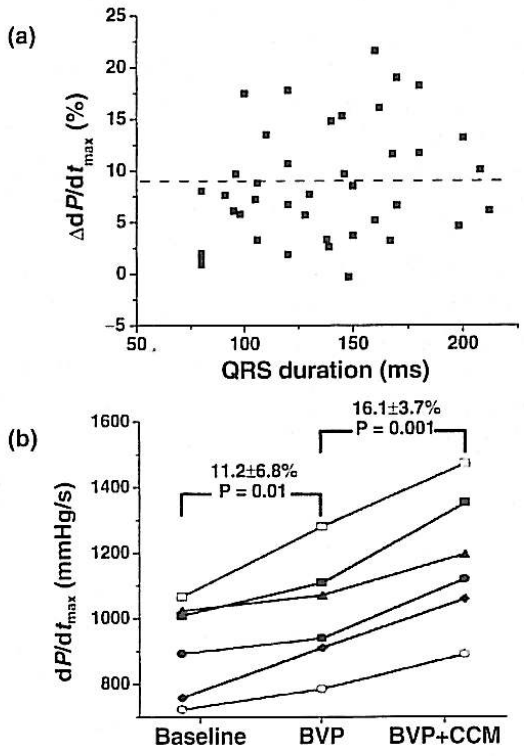

Figure 4.6 (a) Acute effects of cardiac contractility modulating (CCM) signals on dP/dt_{max} in patients with heart failure. Average CCM effect (dashed line) was independent of QRS duration. (b) In patients with prolonged QRS duration, CCM effects were additive to those of biventricular pacing (BVP). (Reproduced with permission from [34]).

Another study examined the impact of acute CCM signal application on myocardial oxygen consumption [36]. 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 VO_2 averaged 13.9 ± 2.3 mL O_2/kg/min. The results showed that myocardial oxygen consumption was 13.6 ± 9.7 mL O_2/kg/min at baseline versus 12.5 ± 7.2 mL O_2/kg/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

In the clinical setting, CCM signals are delivered to the heart by an implantable pulse generator that looks like a pacemaker and connects to the heart via standard commercially available pacing leads (Figure 4.7). The device, called the OPTIMIZER System [37], does not have pacing or antitachycardia therapy capabilities but is designed to work in concert with pacemakers (including CRT devices) and internal defibrillators. The implantable pulse generator has a rechargeable battery that the patients recharge at home once per week via a transcutaneous energy transfer charging unit. In addition, the system includes an acute monitoring system used to measure hemodynamic responses during the system implant and the system programmer.

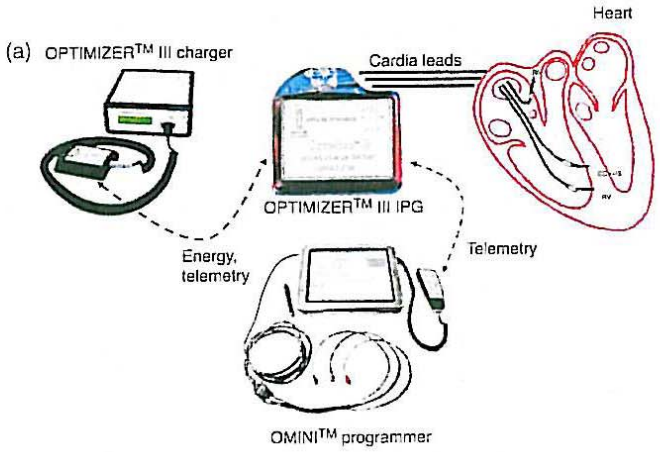

Figure 4.7 (a) System overview with the implantable pulse generator, the leads connecting to the heart, the charger and charging wand, the acute hemodynamic monitoring system used to measure hemodynamic responses during the system implant, and the programmer. (b) Right anterior oblique (RAO) and left 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 midway 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 patient's left, into the septum. A micromanometer (Millar) is placed temporarily to measure physiologic response to acute CCM signal application.

The implant procedure is also similar to that of a standard dual chamber pacemaker and has been described in detail previously, along with a detailed description of the system [5]. In brief, a pocket is 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 as part of an arrhythmia detection algorithm that inhibits CCM signal delivery during arrhythmias. The other two electrodes are positioned on the right ventricular (RV) septum. The electrodes are positioned under fluoroscopic guidance approximately halfway between the base and the apex; one ideally placed near the anterior interventricular groove and the other in the posterior groove (Figure 4.7).

Chronic signal application in heart failure patients

The initial experiences with chronic CCM signal applications were reported in two papers describing results obtained in patients with New York Heart Association (NYHA) class III symptoms and QRS duration $\leq$ 120 milliseconds [37,38]. The study described in these reports (the FIX-HF-3 study) were multicenter, unblinded, uncontrolled, treatment only, feasibility studies designed mainly to test the functionality of an implanted device that automatically delivers CCM signals [37,38]. The OPTIMIZER System was implanted in 23 patients with an average age of 62 $\pm$ 9 years who were primarily male (92%) and were split between idiopathic and ischemic cardiomyopathy (41 and 59%, respectively). Baseline EF averaged 22 $\pm$ 7% and Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score averaged 43 $\pm$ 22. Patients were well medicated with diuretics (88%), β-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 8 weeks of treatment; and no overt safety concerns were revealed. In addition, improvements were reported in patient symptoms (assessed by NYHA class), quality of life (assessed by MLWHFQ), and EF.

This was followed by a second feasibility study carried out in the United States (the FIX-HF-5 Phase I study) [39]. Forty-nine subjects with EF $\leq$ 35%, normal QRS duration (105 $\pm$ 15 ms), and NYHA class III or IV despite medical therapy received a CCM pulse generator. Two weeks after implantation, patients were randomized to a treatment group in which their devices were programmed to deliver CCM signals for 5 h/day (n = 25) or to a control group in which the device remained off (n = 24). All patients were followed for 6 months; both patients and investigators were blinded to the treatment group. Evaluations included NYHA, 6-minute walk, cardiopulmonary stress test, MLWHFQ, and Holter. Although most baseline features were balanced between groups, EF (31.4 $\pm$ 7.4 vs 24.9 $\pm$ 6.5%, p = 0.003), end-diastolic dimension (52.1 $\pm$ 21.4 vs 62.5 $\pm$ 6.2 mm, p = 0.01), peak VO_2 (16.0 $\pm$ 2.9 vs 14.3 $\pm$ 2.8 mL O_2/kg/min, p = 0.02), and anaerobic threshold (12.3 $\pm$ 2.5 vs 10.6 $\pm$ 2.4 mL O_2/kg/min, p = 0.01) were all worse in the treatment group as compared to the control group. Nevertheless, there was 1 death in the control group and more treatment group patients were free of hospitalization for any cause at 6 months (84% vs 62%; Figure 4.8b). Compared to baseline, changes in 6-minute walk (13.4 m), peak VO_2 (0.2 mL O_2/kg/min), and anaerobic threshold (~0.8 mL O_2/kg/min, Figure 4.8a) were more positive in the treatment group than in the control group. None of these differences was statistically significant because of the small sample size. Nevertheless, despite a distinctly sicker population in the treatment group, no safety concerns emerged with chronic CCM signal administration and there were trends toward better outcomes and improved symptoms in response to CCM treatment.

These feasibility studies were followed by a multicenter randomized, double blind, double crossover study of CCM in heart failure patients with NYHA class II or III symptoms despite optimal medical therapy (the FIX-HF-4 study) [40]. One hundred sixty-four subjects with EF < 35% and NYHA class II (24%) or III (76%) symptoms received a CCM pulse generator. Patients were randomly assigned to Group 1 (n = 80, CCM treatment 3 mo, sham treatment second 3 mo) or Group 2 (n = 84, sham treatment 3 mo, CCM treatment second 3 mo). The coprimary endpoints were changes in peak oxygen

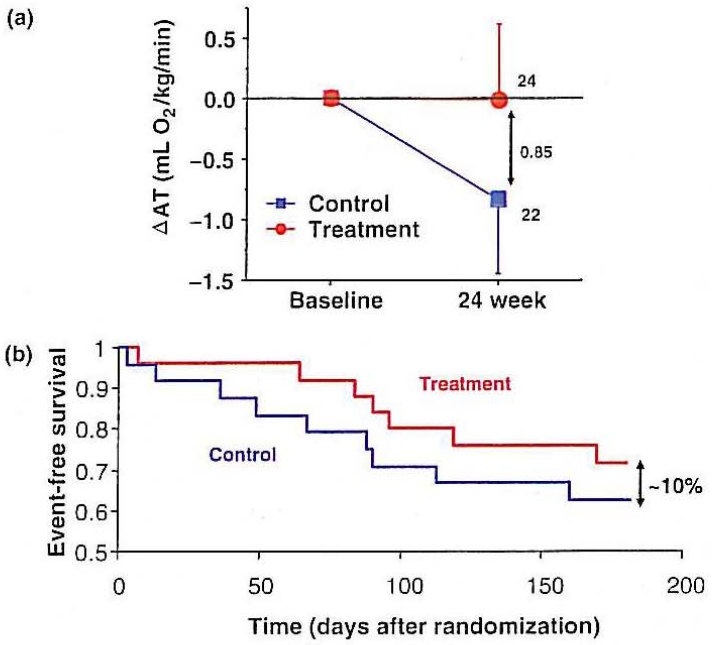

Figure 4.8 Key findings from the US feasibility study (called the FIX-HF-5 Phase I study) of cardiac contractility modulating (CCM). (a) In this prospective, double blind study in which all 49 patients were implanted with an OPTIMIZER System, average anaerobic threshold (measured on cardiopulmonary stress testing) decreased by 0.85 mL O_2/kg/min in the Sham control group and remained constant in the active treatment group. (b) The event-free survival (i.e., the proportion of patients alive without being hospitalized) also trended better in the treatment group. With the small number of patients, the differences were not statistically different. (Reproduced with permission from [39]).

consumption ($VO_{2,peak}$) and MLWHFQ. Baseline EF (29.3±6.69% vs 29.8 ± 7.8%), $VO_{2,peak}$ (14.1 ± 3.0 vs 13.6 ± 2.7 mL O_2/kg/min), and MLWHFQ (38.9 ± 27.4 vs 36.5 ± 27.1) were similar between groups. $VO_{2,peak}$ increased similarly in both groups during the first 3 months (0.40 ± 3.0 vs 0.37 ± 3.3 mL O_2/kg/min) (Figure 4.9a). This was interpreted as evidence of a prominent placebo effect. During the next 3 months, however, $VO_{2,peak}$ decreased in the group switched to sham (−0.86 ± 3.06 mL O_2/kg/min) and increased in patients switched to active treatment (0.16 ± 2.50 mL O_2/kg/min). At the end of the second phase of the study, the difference in peak VO_2 between groups was approximately 1 mL O_2/kg/min. MLWHFQ behaved similarly, trending only slightly better with treatment (−12.06 ± 15.33 vs −9.70 ± 16.71) during the first 3 months (again consistent with a large placebo effect) (Figure 4.9b). During the second 3 months, MLWHFQ increased in the group switched to sham (+4.70 ± 16.57) and decreased further in patients switched to active treatment (−0.70 ± 15.13). Serious cardiovascular adverse events were tracked carefully in both groups. The most frequently reported events were episodes of decompensated heart failure, atrial fibrillation, bleeding at the OPTIMIZER System implant site, and pneumonia. Importantly, there were no significant differences between ON and OFF phases in the number or types of adverse events.

Hospitalizations and mortality were compared for the first period of the study (since these will be difficult to interpret following crossover). In all, there were 14 hospitalizations in Group 1 patients (CCM ON phase) compared to 20 hospitalizations in Group 2 patients (CCM OFF phase). In addition, there was 1 death in a Group 2 patient versus no deaths in Group 1 patients. With the relatively small sample size, the overall event-free survival (Figure 4.9c) did not reach statistical significance ($p = 0.31$), but showed trends of magnitude that were similar to those reported for CRT [1].

In aggregate, the data from the feasibility and larger randomized FIX-HF-4 study show that in patients with heart failure and LV dysfunction, CCM signals appear to be safe and improve exercise tolerance and quality of life.

Currently, a randomized, 12-month, parallel group study that enrolled 428 patients with NYHA class III or IV despite optimal medical therapy is underway at 50 centers in the United States (the FIX-HF-5 Phase II study).

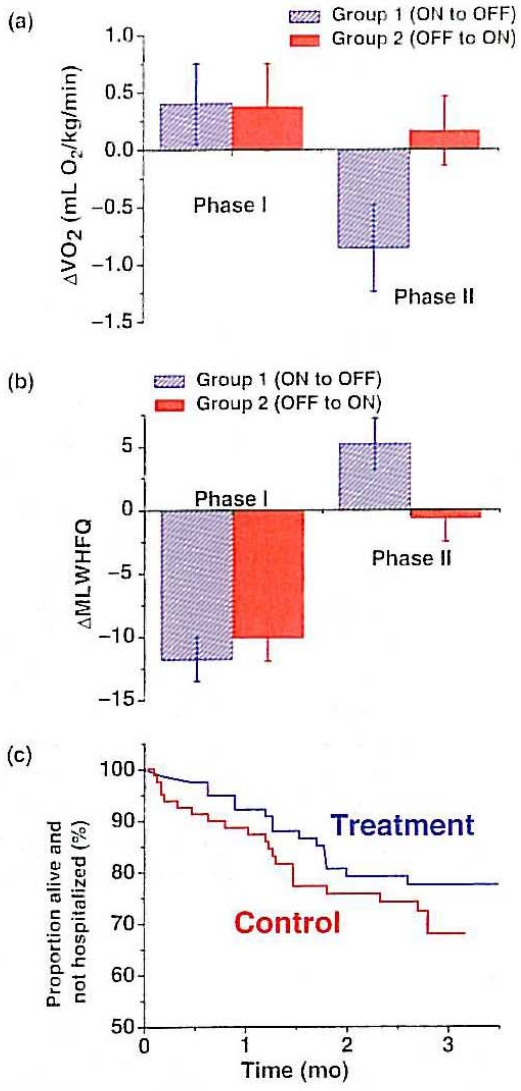

Figure 4.9 Key results of the FIX-HF-4 study [40]. (a) Changes in peak VO_2 between baseline and end of Phase I (labeled "Phase I") and changes between end of Phase I and end of Phase II (labeled "Phase II"). (b) Changes in MLWHFQ with the same format as in (a). For both, parameters were significant but similar during the study Phase I, which was attributed to a placebo effect. Clinically and statistically significant differences emerged between the groups during the second phase of the study, which revealed treatment benefits. (c) Kaplan–Meier analysis of the proportion of patients surviving without being hospitalized during the first phase of the study between baseline and end of Phase I (labeled "Phase I") and changes between end of Phase I and end of Phase II (labeled "Phase II"). Bar graphs of VO_2, MLWHFQ, and event-free survival. With the relatively small number of patients, the differences were not statistically significant.

Evidence of molecular remodeling in patients with heart failure

To explore mechanisms of CCM effects in patients with heart failure, the effects of CCM therapy on myocardial gene expression were investigated in a substudy of 11 patients of the FIX-HF-4 study described above [41]. Endomyocardial biopsies were obtained at baseline (prior to CCM therapy) and 3 and 6 months thereafter. As detailed above, patients were randomized either to get CCM therapy for the first 3 months followed by sham treatment (Group 1) or to receive sham treatment first followed by active treatment (Group2). mRNA expression was analyzed in core laboratory blinded to treatment sequence. Expression of ANP, BNP, MHC, the SR genes SERCA-2a, PLB, RYR, and the stretch response genes p38 mitogen-activated protein kinase (MAPK) and p21ras was measured using reverse transcription polymerase chain reaction and bands quantified in densitometric units (du). The 3 months' OFF therapy phase was associated with increased expression of ANP, BNP, p38-MAPK, and p21ras and decreased expression of α-MHC, SERCA-2a, PLB, and RYR. In contrast, the 3 months' ON therapy phase resulted in decreased expression of ANP, BNP, p38-MAPK, and p21ras and increased expression of α-MHC, SERCA-2a, PLB, and RYR.

A detailed analysis of the findings pertaining to α-MHC is shown in Figure 4.10. Band intensities were normalized to their respective values obtained in the baseline heart failure state. Data from patients with ischemic and idiopathic cardiomyopathy are shown with dashed and solid lines, respectively. At the end of Phase 1, α-MHC expression increased in Group 1 patients (device ON, Figure 4.10a) and stayed the same or decreased in Group 2 patients (device OFF, Figure 4.10b). After crossover, expression decreased in Group 1 patients when the device was switched off and increased in Group 2 patients when the device was switched on. The overall comparisons are summarized in Figure 4.10c, where results from ON periods and OFF periods are pooled. As shown, there was a statistically significant ~62.7 ± 45.3% increase in α-MHC expression above the heart failure baseline state in response to CCM treatment. As shown in this typical example,

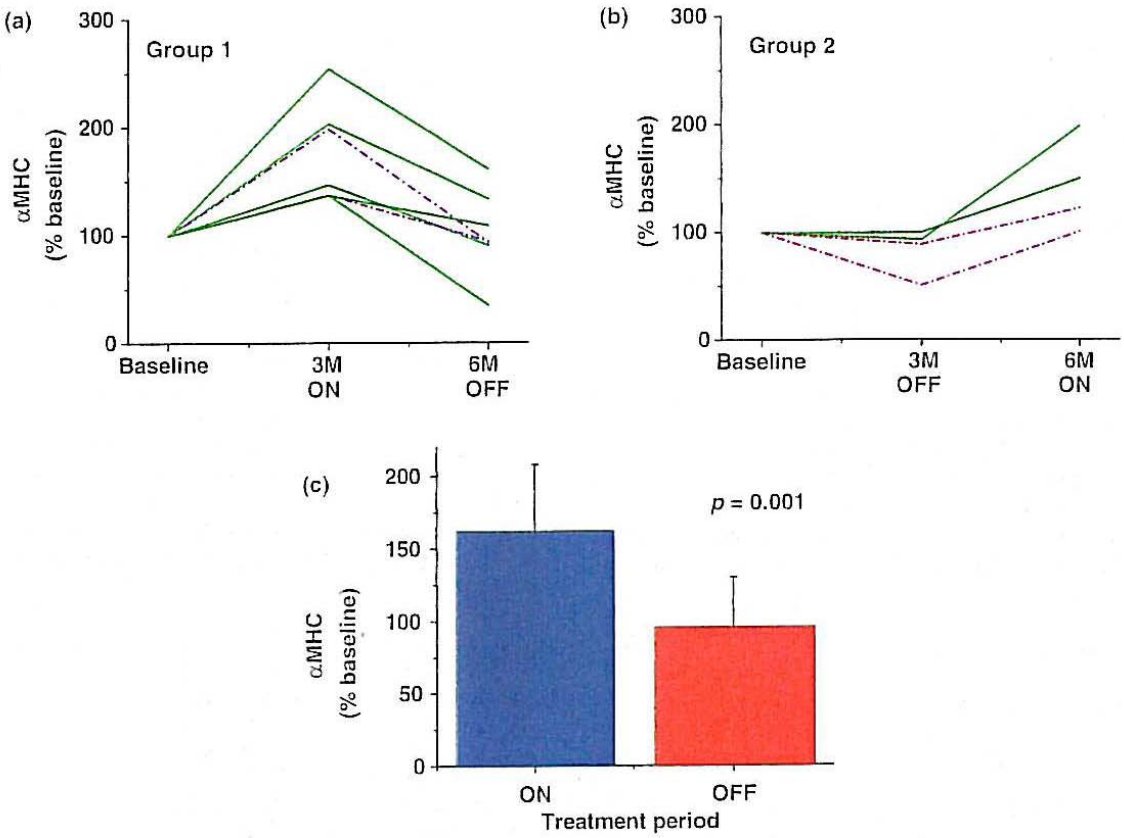

Figure 4.10 Changes in α-MHC (α-myosin heavy chain) expression (quantified as percentage of baseline) at the end of study periods in Group 1 (a) and Group 2 (b) patients. Data summarized by pooling of the end of "ON" periods from the two groups and end of "OFF" periods from the two groups (c). Solid lines show data from patients with idiopathic cardiomyopathy whereas dashed lines are from patient with ischemic cardiomyopathy [41].

there was no substantive difference in the response identified in hearts with idiopathic and ischemic cardiomyopathies. These findings were representative of those obtained with the other genes examined except, as detailed above, expression of ANP, BNP, p38-MAPK, and p21ras were decreased during CCM therapy.

Most interestingly, there were significant correlations between improvements in gene expression correlated with improvements in peak VO_2 and MLWHFQ [41]. As one example, the correlations between changes in these parameters of functional status and changes in SERCA2a expression are summarized in Figure 4.11. As shown, these correlations were present for both ischemic and idiopathic cardiomyopathy.

These findings indicated that CCM treatment reversed cardiac maladaptive fetal gene program and normalized expression of key SR Ca^{2+} cycling and stretch response genes. These findings, which are confirmatory of those identified in response to CCM treatment in animals with heart failure discussed above, support a novel mechanism of action by which CCM improves LV function in patients with heart failure.

Combining CCM with CRT

As discussed above, CCM signals applied in the acute setting to heart failure patients simultaneously receiving CRT provide additive effects on LV contractility indexed by dP/dt_{max}. Because symptoms persist in more than ~30% patients with prolonged QRS duration receiving CRT, we have postulated that addition of CCM treatment may provide an option for these patients. We have previously reported on the initial experience of combining CCM in CRT nonresponders [42]. It was

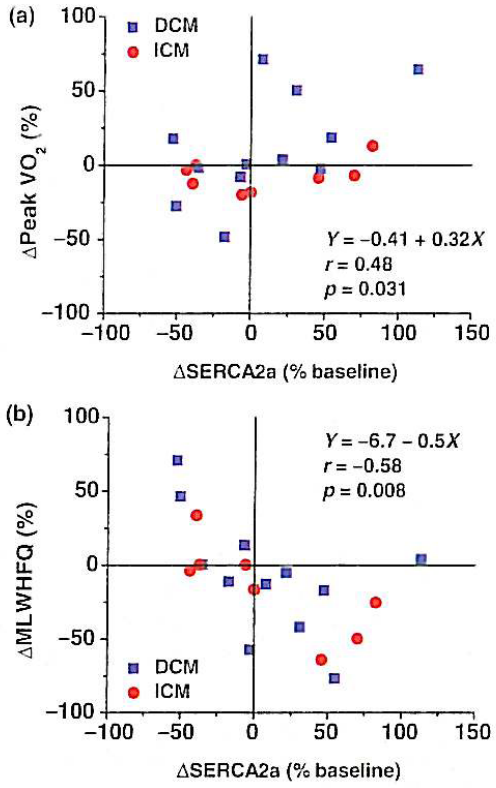

Figure 4.11 Changes in (a) peak VO_2 and (b) MLWHFQ score versus changes in expression of SERCA2a from the subset of 11 patients of the FIX-HF-4 study [41]. DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy.

demonstrated that the implantation procedure is technically feasible, that the OPTIMIZER System and CRT-D devices can coexist without interference, and that acute hemodynamic and clinical improvements can be observed. These preliminary results have provided the impetus for initiation of a prospective study that is now planned to systematically investigate the effects of CCM in CRT nonresponders.

Summary and conclusions

Studies of CCM signals performed in isolated muscle strips and in intact hearts of animals with congestive heart failure have suggested that these signals can enhance myocardial contractile strength. CCM signal delivery with a pacemaker-like device connected to the heart with standard pacing leads has been shown to be straightforward to implement clinically. More recent basic research has demonstrated that CCM signals effect significant changes in myocardial gene expression (including a reversal of several aspects of the fetal gene program expressed in heart failure), improved expression and phosphorylation of the sodium–calcium exchanger and connexin 43, and improved ratio of total PLB to phosphorylated PLB [33,41]. These findings point toward novel mechanisms of action of this electrical form of treatment.

Results obtained in patients with symptomatic heart failure with reduced EF have been encouraging and support both safety and efficacy. A large, randomized, controlled clinical trial is underway in the United States. Future studies could also evaluate whether CCM is effective in patients with wide QRS who declare themselves nonresponsive to CRT [42] 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, anti-tachycardia therapies, and CCM.

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