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Cardiac contractility modulation in patients with advanced heart failure

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Cardiac contractility modulation (CCM) is a novel device-based therapy for heart failure that involves applying electrical signals during the absolute refractory period of the myocardial action potential. This therapy has been shown to augment the strength of left ventricular contraction independent of myocardial oxygen consumption in animal models as well as human studies of patients with heart failure and reduced ejection fractions. The mechanism underlying CCM is an alteration of myocardial calcium handling in a fashion that extends beyond the traditional pharmacological effects of inotropic agents. Analysis of myocardial tissue from both animal models and human hearts treated by CCM demonstrates a shift of abnormally expressed genes towards normal function, positively affecting pathways involving proteins that regulate calcium cycling and myocardial contraction. CCM effects are proven to be independent of QRS duration; however, clinical studies to date have primarily focused on patients with normal QRS since cardiac resynchronization therapy is a well-established option for patients with heart failure and a prolonged QRS duration. Clinical trials show that CCM improves exercise tolerance, as measured by $VO_{2,peak}$ and quality of life, assessed by the Minnesota Living with Heart Failure Questionnaire. The device is currently available for the treatment of heart failure in Europe. Approval in the USA is pending additional testing currently underway using a protocol approved by the US FDA.

KEYWORDS: cardiac • CCM • contractility • heart failure • modulation • optimizer • resynchronization

Cardiac resynchronization therapy (CRT) is a well-established therapy for patients with advanced heart failure and ventricular conduction delay. This device-based therapy is aimed at restoring optimal atrioventricular and inter-ventricular mechanical timings, and has been proven to improve several metrics of advanced heart failure such as symptoms, quality of life (QoL), exercise tolerance and hospital admissions [1,2]. Currently, the traditional marker of dyssynchrony is a left bundle branch-like inter-ventricular conduction delay causing QRS prolongation on a surface ECG. Attempts to identify other markers of mechanical dyssynchrony and CRT response, such as echocardiographic parameters, have thus far proven unsuccessful [3]. Furthermore, patients with mechanical dyssynchrony identified by tissue Doppler imaging in the setting of a normal QRS duration did not benefit from CRT [4]. Thus, left ventricular conduction delay defined by a QRS duration greater than 120 ms currently remains the

main selection criteria for CRT. Results of a large, randomized, multicenter study looking at CRT benefits in narrow QRS patients may expand criteria, but enrollment is currently ongoing and results are presently unavailable [101]. In the absence of expanded CRT criteria, nearly two-thirds of patients with heart failure do not qualify for device-based therapy given a normal QRS duration [5]. Moreover, among those with a prolonged QRS, at least 30% who have received CRT devices show no response to treatment [1]. Therefore, a large portion of the heart failure population remains in need of a new device-based therapy.

Cardiac contractility modulation (CCM) devices provide a novel treatment strategy by generating electrical impulses timed to reach the ventricle during the absolute refractory period. These signals do not alter normal electrical and mechanical sequences and have been shown to improve ventricular contraction with subsequent improvement in exercise tolerance and QoL [6,7].

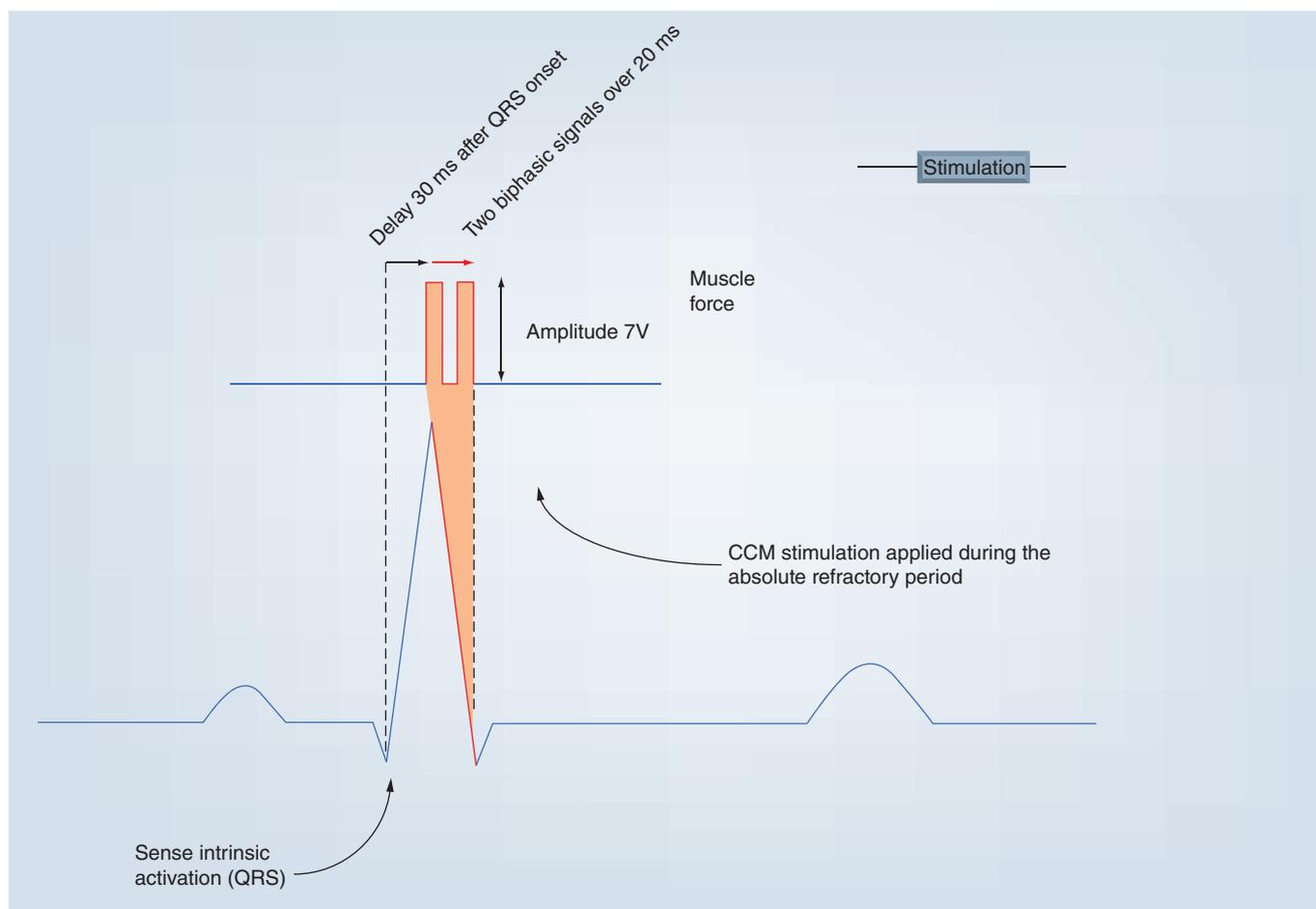


Figure 1. Cardiac contrarily modulation signals are delivered during the absolute refractory periods of cardiac cycles and consist of two high-energy biphasic pulses.

Effects are independent of QRS duration, which makes this technology of great value for patients who are poor candidates for CRT (i.e., narrow or right bundle branch block QRS morphologies); additional added benefits may occur for the CRT-eligible population.

Basic concepts of CCM

CCM signals are delivered during the absolute refractory period approximately 30 ms after the onset of the QRS complex. Signals consist of two biphasic $\pm 7V$ pulses for a total duration of approximately 20 ms (FIGURE 1). Since these signals are timed to stimulate the myocytes while they are in the absolute refractory period, no new electrical or mechanical activations are elicited. Thus, CCM signals are referred to as 'nonexcitatory' as they do not disrupt normal conduction sequences or trigger ventricular arrhythmias.

Similar to conventional cardiac pacing technology, CCM signals are provided by an impulse generator (Optimizer III, Impulse Dynamics, NY, USA) that is implanted in the upper chest area. The impulse generator is connected to the right ventricular septum through two standard active fixation leads and to the right atrium via a single lead designed to detect atrial electrical activity (FIGURE 2). A built-in algorithm in the pulse generator

ensures coupling of sensed atrial and ventricular activities with paced ventricular events. The device detects the onset of atrial and ventricular activations and provides right ventricular stimulations in a fashion that guarantees well-timed delivery in the refractory period. Furthermore, by sensing intrinsic activations, the device recognizes patterns of regular cycles, which will allow stimulatory signals to be withheld in the cases of rhythm disturbances such as ventricular arrhythmias. CCM devices and leads can be successfully implanted in patients with previously implanted cardiac pacemakers or cardiac defibrillators. The CCM device and leads are implanted via the same techniques as standard cardiac devices but are generally placed on the other side of the chest to avoid crowding of accessed veins (FIGURE 3). In contrast to standard pacing signals, CCM delivers 50–100-times the energy. CCM signals can be seen as two electrical artifacts on the surface ECG with no other impact upon the appearance of patient's baseline ECG (FIGURE 4A & B).

CCM effects on hemodynamics & myocardial energetics

CCM effects on enhancement of cardiac function are rather acute and can be detected shortly after application of therapy.

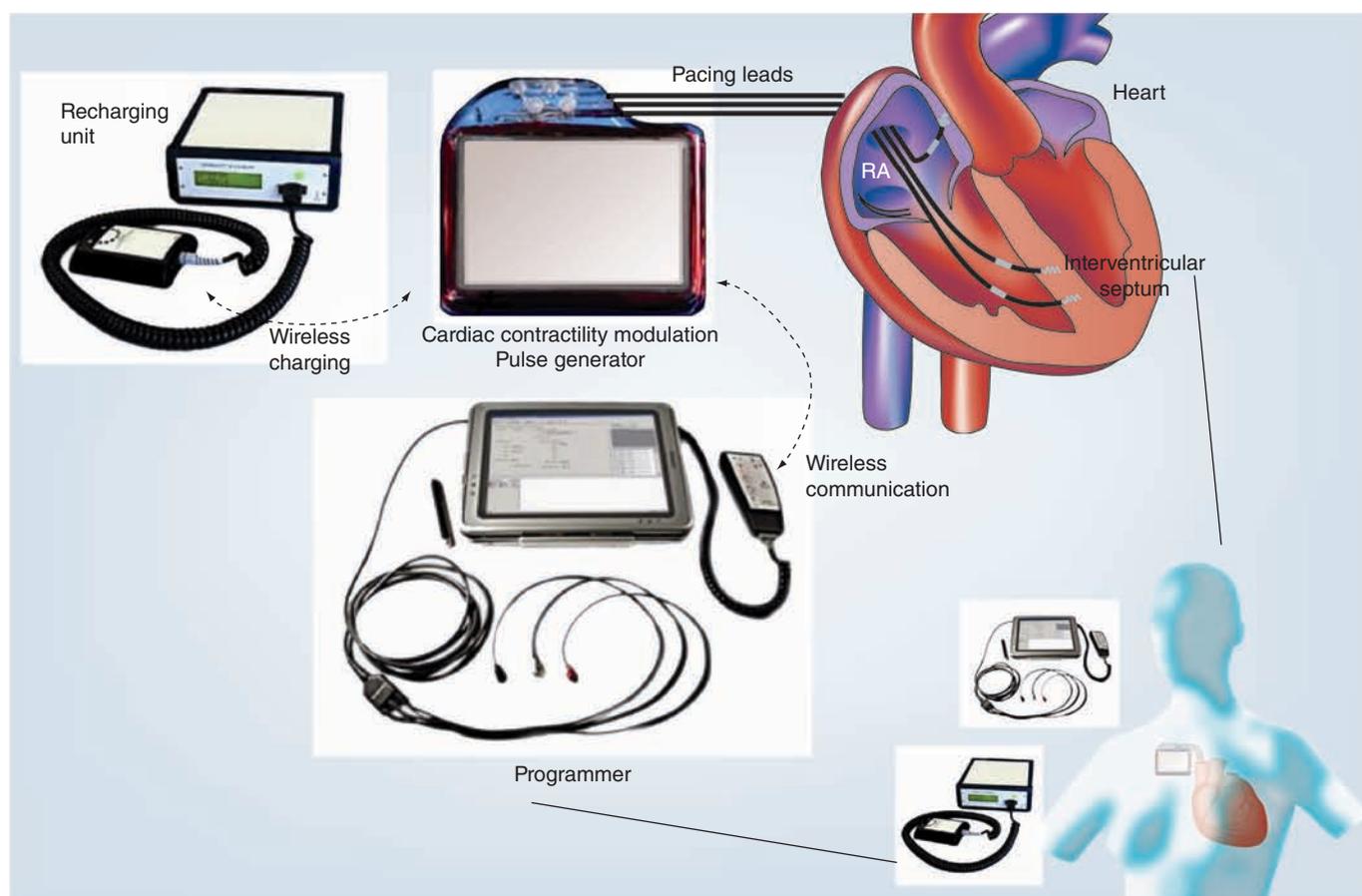


Figure 2. Basic components of the cardiac contraction modulation system, including wireless recharging components and the control unit.

Prior studies have shown that left ventricular contraction strength, indexed by left ventricular pressure and rate of pressure rise (dp/dt_{max}), improve within minutes after the onset of CCM signal delivery [7-11]. These favorable acute hemodynamic changes are independent of QRS duration [12,13]. Interestingly, when applied concurrently with CRT, the benefits were additive [12], supporting a unique mechanism of action that may extend to CRT nonresponders.

Improvement in cardiac function without an increase in myocardial oxygen demand is the ultimate goal of heart failure therapy from safety and efficacy standpoints. In order to investigate the relationship in CCM patients, myocardial oxygen consumption was measured in nine patients undergoing therapy. A 20% acute increase in contractility (assessed by dp/dT) was seen while oxygen consumption remained unchanged [14]. Comparatively, one study treated patients with dobutamine in oscillating doses to match the same increase in dp/dT achieved with CRT. Dobutamine attained an effect that matched CRT-based hemodynamic improvement, but was associated with increased oxygen consumption compared with CRT that did not cause a rise in energy cost; in fact, it modestly lowered it [15]. Thus, CCM's neutral effect on myocardial energy demand is similar to CRT but distinctly different from inotropic drugs.

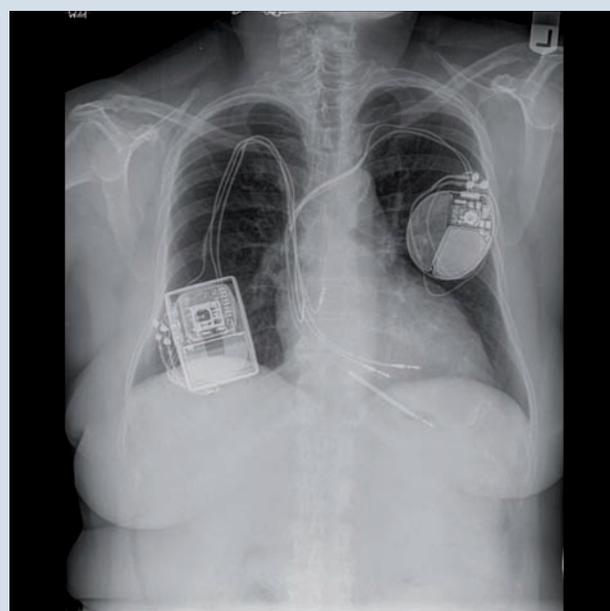


Figure 3. Chest x-ray of a patient implanted with cardiac contractility modulation pulse generator/leads (right) and implantable cardiac defibrillator/leads (left).

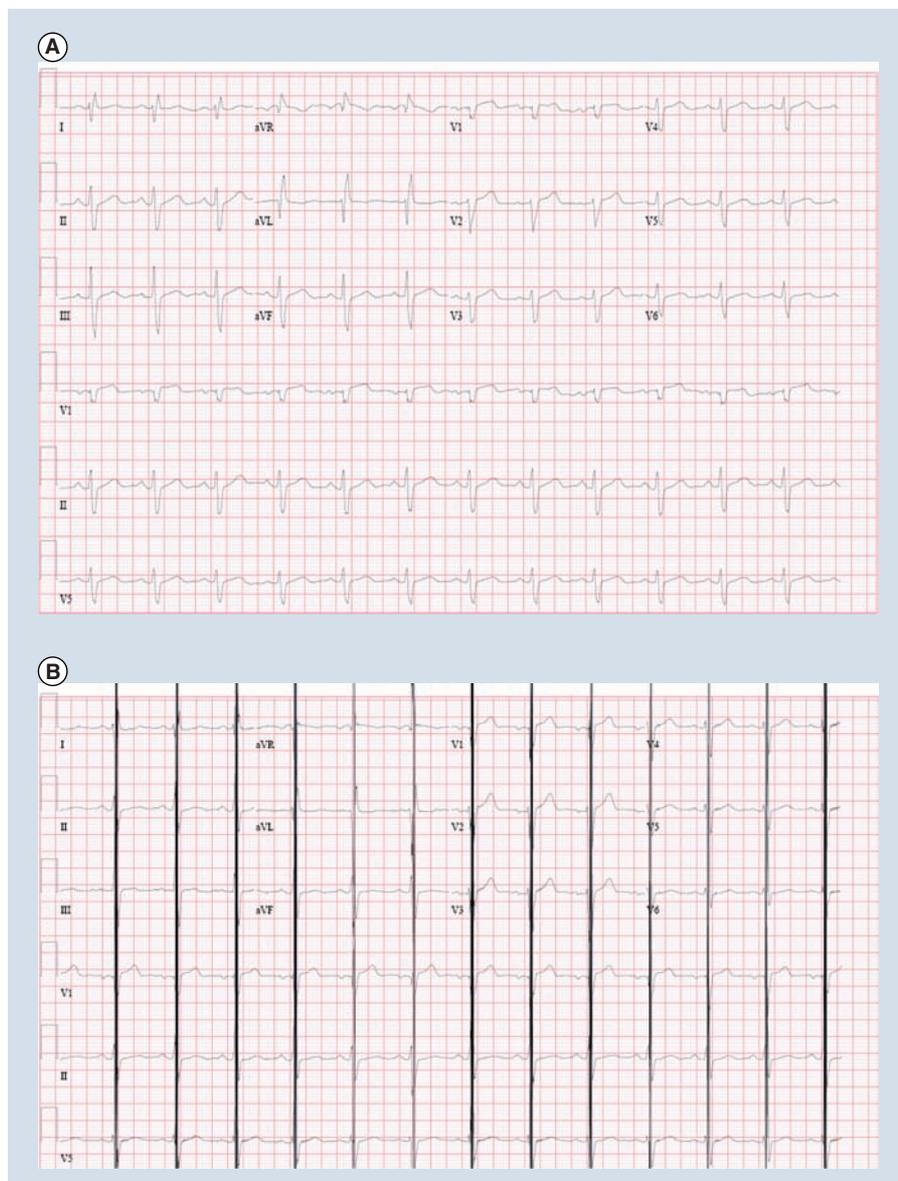


Figure 4. Electrocardiograms in a patient implanted with the cardiac contractility modulation device. (A) Baseline 12-lead ECG from a patient implanted with a cardiac modulation device before receiving cardiac contractility modulation stimulation. **(B)** 12-Lead ECG of the same patient, now receiving active cardiac modulation stimulations. Noncapturing ventricular artifacts are noted throughout. Note that the signals do not initiate new contractions or modify activation sequences.

CCM effects on cardiac function

CCM benefits are not limited to acute improvements in cardiac hemodynamics but expand further by enhancing reverse remodeling and augmenting global ventricular function with chronic stimulation [16,17]. In a study of 30 patients with left ventricular ejection fractions (LVEFs) <35% and New York Heart Association (NYHA) functional class III symptoms despite optimal medical therapy, 3-month CCM therapy was associated with a 5% absolute increase in LVEF. Furthermore, end-diastolic and end-systolic volumes decreased by approximately 12 and 7 ml, respectively, suggesting that CCM can influence beneficial structural changes

beyond levels achieved by optimal medical therapy alone.

Mechanisms of action

The mechanism by which CCM increases contractility without affecting myocardial energetics is believed to be related to its unique property of favorably altering key regulatory gene expression and protein–protein interactions. This proposed theory is supported by the results of prior published work that investigated the cellular responses to electromagnetic (EM) fields [18]. Such work proposed that EM interaction with electrons in DNA molecules, especially in H-bonds, could possibly modify genetic function. Furthermore, DNA modulations and subsequent biochemical responses are believed to vary with the application of different EM frequencies, durations and electrical stimulation types [18].

In this regard, studies in animal models have investigated the acute and chronic effects of CCM therapy on several genes and key regulatory proteins known to be adversely altered in heart failure. In these studies, tissue samples obtained from locations close to the CCM delivery site along the interventricular septum, as well as from remote areas in the left ventricular free wall, were subjected to extensive molecular and biochemical analysis [10,11]. Interestingly, within minutes of CCM signal delivery, tissue obtained from areas close to the stimulation site in canine models demonstrated increases in phosphorylation of the essential PLB protein. Phosphorylated PLB reduces an inhibitory effect on SERCA2a, which is the key pump controlling calcium release from the sarcoplasmic reticulum. This action leads to a rise in calcium levels and increases contractility [11]. It is well known that SERCA2a expression decreases in chronic heart failure; however, after only a few hours of CCM stimulation, *SERCA2a* gene expression regionally close to signal delivery sites improves. The same increase was seen over time at remote locations following chronic stimulation. Similar phenomena are noted in *BNP* gene expression. In contrast to *SERCA2a*, *BNP* gene expression is increased in chronic heart failure and tends to normalize with CCM stimulation.

Several other well-studied regulatory proteins known to be altered in heart failure have been investigated in tissue samples obtained from canine models, both from sites close to CCM stimulation and from remote areas of the left-ventricular free wall [11]. Compared with dogs that received sham stimulation,

those receiving active CCM signals had increased levels of β_1 adrenergic receptors, SERCA2a, P-PLB and ryanodine receptors. Concurrently, levels of ANP and BNP decreased significantly. Interestingly, total PLB levels did not change with CCM; however, the levels of the active phosphorylated form were significantly higher in the CCM group. While normalization of gene expression at areas of the myocardium adjacent to the CCM stimulation site can be explained by the direct effects of the electrical signals, further investigations are needed to fully understand the changes seen in remote areas of the myocardium. Theorized explanations include propagation of electrical signals through gap junctions to remote areas or expansion of regional improvements to overall improvements in cardiac function mediated by favorable hemodynamics.

The molecular effects of CCM therapy were studied in a subgroup of 14 human subjects participating in the FIX-HF-4 clinical trial. Patients were divided into two groups: group 1 was treated with active CCM for 3 months followed by sham treatment for 3 months, while group 2 was treated in the reverse order. Endomyocardial biopsies were obtained from both groups at baseline, 3 and 6 months. Gene expression was then tested in a blinded fashion.

The results of this study showed that CCM tends to favorably change gene expression, which is abnormally regulated in a chronic heart failure state. The 3-month sham phase was associated with decreased expression of α -myosin heavy chain, SERCA-2a, PLB and ryanodine receptors, while 3 months of active CCM therapy drove gene expression of these proteins, which are essential for calcium metabolism, toward normality [19]. These human findings highlight the unique mechanism by which CCM stimulation alters calcium handling with subsequent improvements in contractility and overall cardiac function in heart failure.

CCM in heart failure patients: FIX-HF-4 study

The initial clinical application of CCM signals in humans was investigated in small pilot studies that showed promising data [16,20,21]. Based on these results, the FIX-HF-4 study was implemented as the first multicenter, randomized, double-blinded trial in the heart failure population [22]. A total of 164 patients with chronic NYHA functional class II or III heart failure and LVEF $\leq 35\%$, despite optimal therapy, received CCM devices. Patients were randomly assigned to group 1 ($n = 80$) or group 2 ($n = 84$) in a crossover fashion. Group 1 received active CCM for 3 months followed by sham therapy for 3 months, while group 2 was treated in the reverse order. Analyses were performed after each treatment period.

At baseline, approximately three out of four of the patients (76%) were in NYHA functional class III. The primary end points were assigned to assess changes in functional capacity,

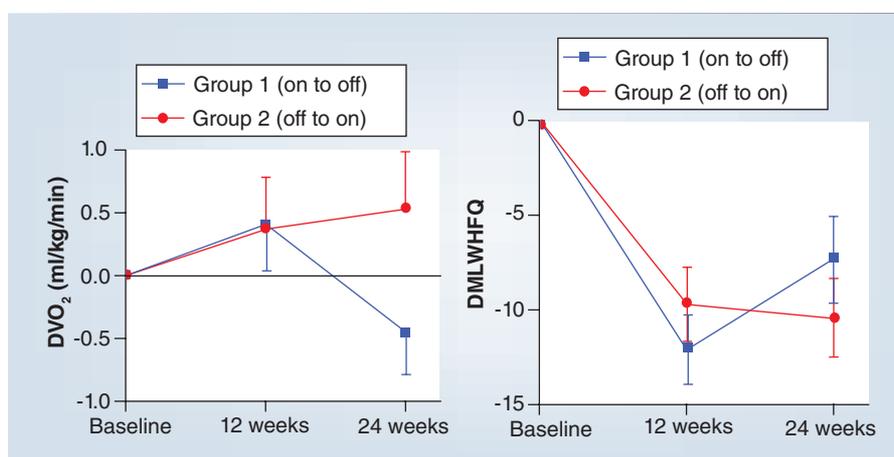


Figure 5. Fix-HF-4 primary end points. A strong placebo effect was noted at 3 months in both $VO_{2,peak}$ and QoL indexed by MLWHFQ. However, at 6 months and after accounting for the crossover study design, statistical analyses favored active treatment in both $VO_{2,peak}$ ($p = 0.030$) and MLWHFQ ($p = 0.030$). MLWHFQ: Milwaukee Living with Heart Failure Questionnaire; QoL: Quality of life. Reproduced with permission from [22].

indexed by changes in peak oxygen consumption ($VO_{2,peak}$), and changes in QoL, assessed by Milwaukee Living with Heart Failure Questionnaire (MLWHFQ). Baseline characteristics were equal in both groups: LVEF was 29.3 versus 29.8%, $VO_{2,peak}$ was 14.1 versus 13.6 ml/kg/min and MLWHFQ was 38.9 versus 36.5 points for each group, respectively.

Regardless of therapy received, $VO_{2,peak}$ increased to the same degree in both groups during the first 3-month period (0.40 vs 0.37 ml/kg/min), which was attributed to a profound placebo effect. However, in the following 3 months, $VO_{2,peak}$ increased in CCM treated patients (0.16 ± 2.50 ml/kg/min) and decreased in the sham treatment group (-0.86 ± 3.06 ml/kg/min). At the end of the second phase, and after incorporating carryover and period effects into the statistical analyses, a significant $VO_{2,peak}$ net increase (0.52 ± 1.39 ml/kg/min; $p = 0.032$) was noted with CCM therapy.

QoL measures acted in a similar fashion to $VO_{2,peak}$ with improvement in both arms during the initial phase of the study attributed largely to a placebo effect. MLWHFQ scores trended down (lower numbers indicate better QoL) and slightly favored the active arm (-12.06 vs -9.70 points). However, during the second phase of the study, MLWHFQ differences between the two arms were more pronounced; scores increased in the sham group ($+4.70$ points) and decreased in those receiving CCM (-0.70 points). After accounting for the crossover study design, statistical analyses showed a favorable treatment effect ($p = 0.030$) (FIGURE 5).

There were no significant differences in reported adverse events between the active and sham phases. Adverse events recorded included decompensated heart failure, atrial fibrillation, bleeding at the implant site and pneumonia. Overall, this study met its primary end point with improvements in both exercise tolerance and QoL during the active period of treatment without any difference in adverse effects.

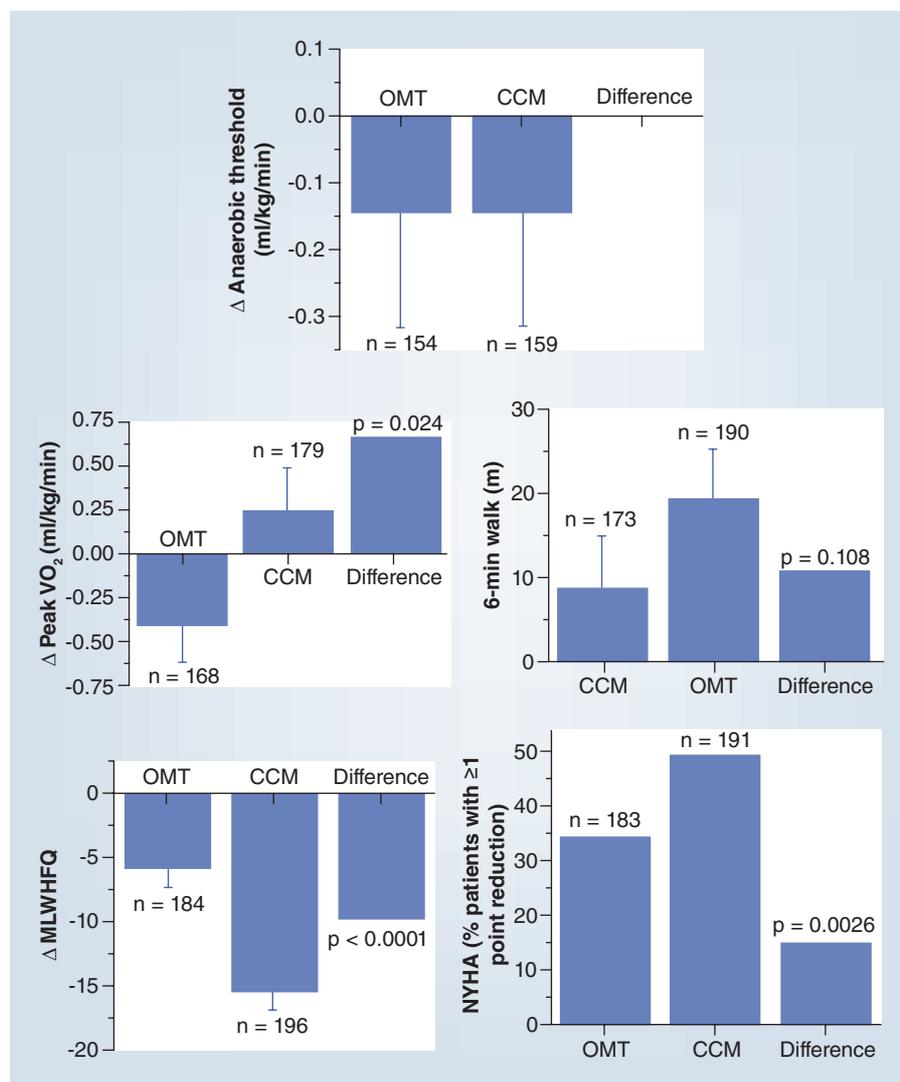


Figure 6. Fix-HF-5 efficacy end points. The study did not meet its primary efficacy end point (ventilatory anaerobic threshold). Secondary efficacy end points, however, including VO_2 peak and MLWHFQ scores, favored the cardiac contractility modulation group.

MLWHFQ: Milwaukie Living with Heart Failure Questionnaire. Reprinted with permission from [37].

FIX-HF-5 study

Following these promising results, the FIX-HF-5 study was conducted across nearly 50 sites in the USA and was the largest CCM clinical trial to date [23]. Four hundred and twenty eight patients with NYHA functional class III (89%) and IV (11%) heart failure, a narrow QRS (mean: 101 ms) and an LVEF <35% (mean: 25%) despite stable optimal medical therapy (OMT) were enrolled. Patients were randomized in a 1:1 fashion to receive OMT plus CCM ($n = 215$) or OMT alone ($n = 213$). The primary safety end point was a composite of all-cause mortality and all-cause hospitalizations at 12 months. Efficacy end points included change in exercise tolerance and QoL at 6 months compared with baseline, as assessed by a noninferiority comparison.

Exercise tolerance was assessed by the ventilatory anaerobic threshold (VAT), which is the point in exercise when ventilation starts to increase in a nonlinear fashion and is believed to take place when energy supply is shifted from the aerobic energy system (mitochondrial respiration) to anaerobic energy systems (glycolysis and the phosphagen system). At the time of study initiation, the VAT was not a widely used parameter in clinical trials. Its inclusion as a primary end point was recommended by the US FDA due to the unblinded study design and the decreased susceptibility of the VAT to placebo effect (compared with $VO_{2,peak}$). The primary efficacy end point was a percentage comparison of responders in each group (CCM + OMT vs OMT alone). Responders in each group were defined as patients who would achieve an increase in VAT of more than 20% [24]. Similar to FIX-HF-4, MLWHFQ scores were used to assess QoL. Two aspects of the study design (VAT as an end point and 'responder analyses') were new concepts in heart failure trials and imposed significant statistical challenges for the study [24,25].

The study groups were well matched in baseline characteristics; heart failure etiology was mostly ischemic, accounting for nearly two-thirds of both OMT and CCM groups (67 vs 65%, respectively). Both OMT and CCM groups were similar in age (58 ± 13 vs 59 ± 12 years, respectively), baseline VAT (11.0 ± 2.2 vs 11.0 ± 2.2 ml/kg/min, respectively), and $VO_{2,peak}$ (14.7 ± 2.9 vs 14.8 ± 3.2 ml/kg/min, respectively).

The study met its safety end points of all-cause mortality and all-cause hospitalizations. After nearly 1-year follow-up,

103 adverse events were reported in the OMT group (52%) and 112 in the CCM group (48%). Statistical tests, including the Blackwelder test of noninferiority ($p = 0.034$) and the Log-Rank test ($p = 0.22$), confirmed the findings.

The study did not meet its primary efficacy end point as changes in VAT were not statistically different between groups. The study remained negative regardless of analyses carried out based on responder percentages in each group or mean changes in VAT. However, secondary efficacy end points including $VO_{2,peak}$ and MLWHFQ scores were significantly improved in the CCM group. In the CCM group, $VO_{2,peak}$ was 0.7 ml/kg/min greater ($p = 0.024$) and MLWHFQ was 9.7 points better ($p < 0.0001$) compared with the control group (FIGURE 6).

Per the study protocols, efficacy end points were allowed to be explored in specific patient subgroups for the purpose of hypothesis

generation [26]. When examining patients with LVEF $\geq 25\%$ and symptoms classified as NYHA functional class III (97 OMT and 109 CCM patients, comprising almost half of the entire study population), changes in VAT, $VO_{2,peak}$ and QoL measures were more pronounced and in favor of the treatment arm. More specifically, among CCM patients, VAT was improved by 0.64 ml/kg/min ($p = 0.03$), $VO_{2,peak}$ was greater by 1.31 ml/kg/min ($p = 0.001$) and MLWHFQ was better by 10.8 points ($p = 0.003$) compared with the OMT patients (FIGURE 7).

Responder analyses in this subgroup also demonstrated that 5.8% of OMT and 20.5% of CCM patients met the preset $\geq 20\%$ increase in VAT, with a net difference of 14.7% at the 6-month follow-up mark ($p = 0.007$). The abovementioned effects on exercise capacity and QoL in this subgroup were maintained for the entire 12-month follow-up period of the study. Subgroup analysis was considered retrospective as per the study protocol; however, these findings suggest a positive treatment effect by CCM therapy in patients with an LVEF $\geq 25\%$ and NYHA functional class III. This analysis was the foundation of a new multicenter, randomized, prospective study aimed at capturing these less-sick heart failure patients; the FIX-HF-5B was recently launched in the USA to address this population.

Interestingly, benefits of CCM therapy in patients with less sick hearts (LVEF $\geq 25\%$ and NYHA functional class III) can lead to a better understanding of CCM's mechanisms of action. It has been proven that CCM signals have immediate localized effects on cardiac contractility and with time, these effects extend to enhancing global cardiac function. It is also well known that LVEF decreases as the dimension of the ventricle increases. Based on this principle, it can be hypothesized that CCM effects on global cardiac function diminish as the LV size increases and LVEF decreases due to increased distance from the stimulation site. Another intriguing hypothesis is that severely remodeled ventricles may have excessive fibrosis and non-viable scarring that cannot be influenced to undergo positive gene expression by CCM signals.

In order to further investigate this presumption clinically, a subgroup of 38 patients with a LVEF $\geq 35\%$ were identified from the FIX-HF-5 general population. These patients were initially included in the study after the enrolling site determined their LVEFs to be $\leq 35\%$ by local echocardiography. However, repeat assessment of cardiac function by a core laboratory did not confirm these findings. Among these 38 patients, 18 happened to be in the

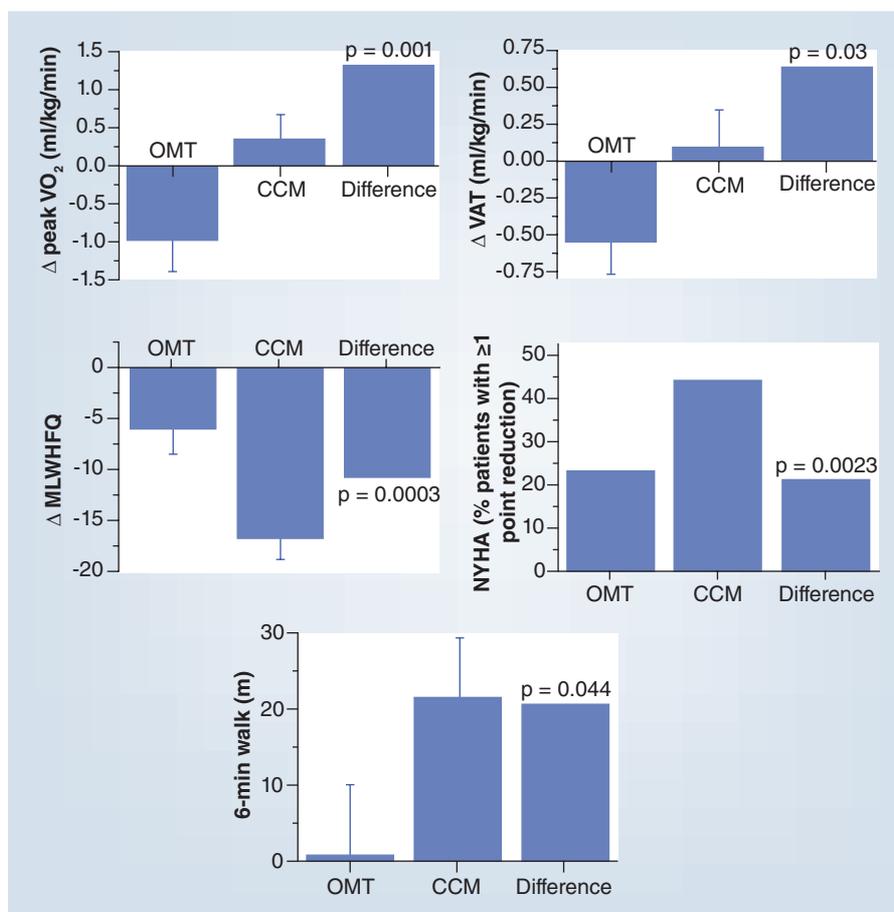


Figure 7. Subgroup analysis of the FIX-HF-5 study. Among patients with LVEF $\geq 25\%$ and symptoms classified as NYHA class III, changes in VAT, $VO_{2,peak}$ and QoL measures were much more pronounced and in favor of the treatment arm. MLWHFQ: Milwaukie Living with Heart Failure Questionnaire; QoL: Quality of life; VAT: Ventilatory anaerobic threshold. Reproduced with permission from [27].

CCM group and 20 in the OMT group. Comparison of the efficacy end points in this selected subgroup were much improved in favor of CCM; with improvements occurring to a greater degree than those seen in the subgroup of patients with LVEF $\geq 25\%$. CCM treatment improved $VO_{2,peak}$ by 2.96 ml/kg/min ($p = 0.03$) and MLWHFQ score by 18 points ($p = 0.06$). VAT was 0.57 ml/kg/min greater in the CCM ($p =$ not significant), which may be explained by the small sample size. These findings support the hypothesis that greater CCM benefits can be seen in patients with moderate, as opposed to severe, LV dysfunction. The aforementioned new FIX-HF-5B study will hopefully answer this question with its recently approved expanded entry criteria to enroll patients with an LVEF between 25 and 45%.

CCM versus CRT

As a novel device-based therapy for heart failure, natural comparisons will be drawn between CCM and CRT. Therefore, it will be of great importance to compare CCM benefits in the narrow QRS population [21,23] to those obtained with CRT in a wide QRS cohort (FIGURE 8) [1,27–31]. Despite the difference in QRS duration,

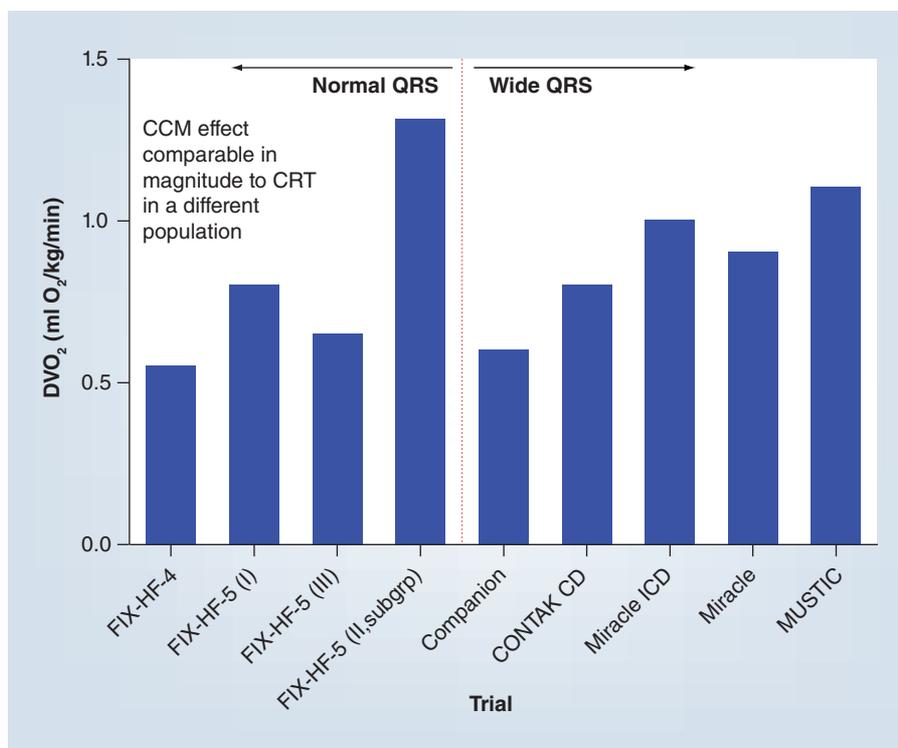


Figure 8. Improvements in exercise capacity indexed by VO_2 peak in cardiac contractility modulation trials (narrow QRS) are comparable with improvements seen in major cardiac resynchronization therapy trials (wide QRS).

CCM: Cardiac contractility modulation; CRT: Cardiac resynchronization therapy. Reproduced with permission from [31].

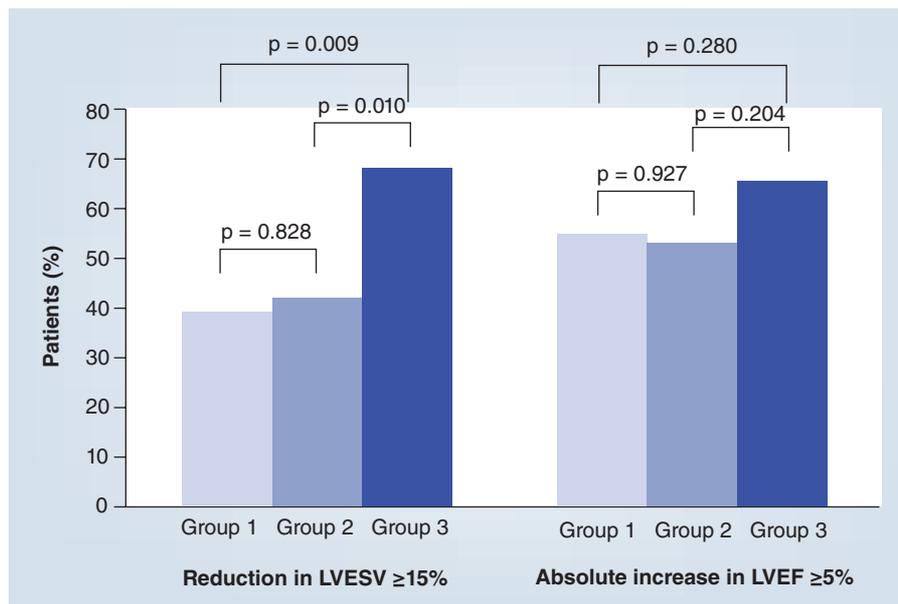


Figure 9. Reverse remodeling responders rate among the study groups; group 1 (cardiac contractility modulation), group 2 (cardiac resynchronization therapy [CRT]; QRS: 120–150 ms), group 3 (CRT; QRS: >150 ms). Response was defined as increase in LVEF $\geq 5\%$ or decrease in LVESV $\geq 15\%$, after 3 months of therapy.

LVEF: Left ventricular ejection fraction; LVESV: Left ventricular end-systolic volume. Reproduced with permission from [34].

patients in CCM trials share many similarities with CRT trial populations: most patients were in NYHA functional class III heart failure with baseline LVEF approximately 25%, had an ischemic etiology of their heart failure and had an average baseline $\text{VO}_{2,\text{peak}}$ of 14 ml/kg/min. Mean age and gender distributions were also similar.

Comparisons show that the benefits of CCM on exercise capacity were similar to those seen in previous CRT trials [31]. In fact, CRT was initially approved for treating heart failure based on early trials demonstrating benefits of improved functional capacity and QoL. Recent CRT trials, however, have expanded the scope of benefits to include mortality and heart failure hospitalization reduction [32,33]. Similar morbidity and mortality data are lacking for CCM, but further investigations are underway in Europe.

A recent study [34] evaluated the extent of left ventricular reverse remodeling in patients treated with CCM compared with those treated with CRT. The studied patients were NYHA functional class III with an LVEF $< 35\%$ despite OMT. They were divided into three groups: group 1 ($n = 33$) included patients who received CCM with QRS < 120 ms, group 2 ($n = 43$) included patients who received CRT with QRS of 120–150 ms and group 3 ($n = 56$) included CRT patient with QRS > 150 ms. Baseline characteristics including heart failure etiology and baseline LVEF were comparable among the groups. Reverse remodeling parameters included echocardiographic assessments of left ventricular systolic volume, left ventricular diastolic volume and LVEF. At 3 months, left ventricular systolic volume and LVEDV decreased while LVEF increased in all three groups. The degree of reverse remodeling was comparable in group 1 and group 2, but was the most pronounced in group 3 ($p < 0.005$). LVESD improvement of $\geq 15\%$ was noted in 39% of group 1, 42% in group 2 and 68% in group 3. Similarly, increases of LVEF $\geq 5\%$ were seen in 55% of group 1, 53% in group 2 and 66% in group 3 (FIGURE 9). Although baseline characteristics were equal, this study was an observational analysis and not a true head-to-head comparison. However, it adds to the body of data supporting CCM's capacity to induce

structural remodeling to a degree comparable to CRT with modest QRS prolongation (120–150 ms). The greatest response seen in patients with very wide QRS >150 ms can be explained by the reversal of electromechanical dyssynchrony that serves as a functional substrate to CRT therapy, in contrast to the narrow QRS patients with severely remodeled hearts who lack dyssynchrony as a therapeutic target. These data add more evidence that CCM functions independently of electromechanical delay and its effects on structural remodeling can be additive to CRT.

CCM added to CRT

Regardless of the QRS duration, CCM signal applications are capable of inducing acute favorable hemodynamic changes and enhancing contractility as measured by the instantaneous rise in dp/dt [12]. It is known that nearly one third of patients who receive CRT do not respond to the therapy. Adding CCM to CRT nonresponders can be a potential therapeutic option for those patients. This concept is still in an early stage of development. One published report has confirmed that implanting a CCM system in a patient who already had a CRT system in place is technically feasible and that function of both devices was maintained without EM interference [35]. Favorable hemodynamic and clinical improvements were observed in the patient. A small pilot study of 16 CRT nonresponders implanted with CCM devices was conducted in Germany [36]; improvement in LV hemodynamics, ejection fraction and NYHA functional class were reported with no interferences between CRT and CCM devices. A new clinical study has been designed to test this theory further in a prospective fashion.

Expert commentary

CCM stimulation is a unique device-based therapy that is making a rapid advancement in the arena of chronic symptomatic heart failure therapy. By using an implantable pulse generator and conventional pacing leads connected to the right atrium and ventricle, electrical impulses are originated and timed to fall onto the refractory period of the QRS complexes, therefore causing no change in normal excitation sequences. Such stimulation is proven to improve regional and global cardiac function and enhance

structural remodeling without increasing metabolic demand. The underlying mechanisms of CCM are related to normalization of key gene expression that is altered in heart failure. Additional mechanisms include improvements in contractility through normalization of key protein phosphorylation, as shown in animal and human models [10,19]. Clinical studies on humans have shown improvement in QoL and exercise capacity in patients with chronic symptomatic heart failure and reduced cardiac function. The benefits of CCM stimulation are independent of the QRS duration, enabling this therapeutic modality to provide an alternative option to CRT nonresponders and perhaps additive benefits to those already receiving CRT.

Five-year view

Approximately 1000 patients have been treated with chronic CCM stimulation around the world thus far. The majority of published CCM clinical trials have focused on patients with symptomatic heart failure, left ventricular dysfunction and narrow QRS, as those patients are not covered by any established device-based therapy guidelines. Randomized clinical studies have shown improvement in exercise tolerance, QoL, NYHA functional class and MLWHFQ scores. The device is already approved in countries that recognize the CE Mark. In the USA, an FDA-approved clinical trial is currently underway to investigate the effect of CCM on VAT in patients with ejection fraction $\geq 25\%$ and NYHA functional class III symptoms despite optimal medical therapy. Data on morbidity and mortality are still lacking, but ongoing investigations are focusing on these areas. Future clinical investigations will study CCM effects among CRT nonresponders and those who are already receiving CRT in a large, randomized, prospective fashion.

Financial & competing interests disclosure

D Burkhoff and WT Abraham are consultants for Impulse Dynamics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Key issues

- Cardiac contractility modulation (CCM) is a novel device-based therapy for the treatment of chronic heart failure.
- CCM delivers high-energy impulses during the absolute refractory period of the myocardial cycle in a fashion that does not affect normal electrical sequences.
- CCM improves cardiac function without increasing myocardial oxygen demand.
- CCM causes otherwise abnormally regulated genes in heart failure to return towards normal expression. These genes play a key role in intracellular calcium handling, myocardial energy utilization and contractility.
- Positive effects of CCM are seen both locally near stimulation sites as well as globally throughout the myocardium with chronic stimulation.
- Clinically, CCM has been shown to improve functional capacity and quality of life in early clinical trials. Ongoing trials continue to investigate efficacy and populations that may receive benefits from CCM.
- CCM benefits are independent of QRS duration. As such, CCM may be an alternative therapy for cardiac resynchronization therapy-ineligible patients and may provide added benefits to cardiac resynchronization therapy responders and nonresponders alike.

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