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REVIEW

Enhancing myocardial function with cardiac contractility modulation: potential and challenges

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Abstract

Cardiac contractility modulation (CCM) offers a novel therapeutic avenue for heart failure patients, particularly those unresponsive to cardiac resynchronization therapy within specific QRS duration ranges. This review elucidates CCM's mechanistic underpinnings, its impact on myocardial function, and utility across patient demographics. However, CCM is limited by insufficient data on mortality and hospitalization rate reductions, as well as the need for specialized device implantation skills. While prevailing research has concentrated on left ventricular effects, a knowledge gap persists for other patient subsets. Future inquiries should address combinatory treatment strategies, extended usage and the impact of atrial fibrillation on device implantation. Such expanded studies could refine therapeutic outcomes and widen the scope of beneficiaries.

Keywords Cardiac contractility modulation; Cardiac devices; Device implantation; Heart failure

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Introduction

Approximately 1% to 2% of the global population suffers from heart failure (HF). It is a leading cause of death worldwide, and it affects over 10% of individuals over the age of 70.[1] HF presents with clinical signs such as moist rales, peripheral oedema, and jugular venous congestion.[2] While there is no single pathological diagnosis for HF, it is considered a clinical syndrome primarily caused by myocardial dysfunction.[2]

The cornerstone treatment strategy for patients with HF and reduced ejection fraction (HFrEF) involves a quadruple therapy regimen, including angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor-neprilysin inhibitors (ARNIs)/angiotensin receptor blockers (ARBs), beta-blockers, sodium-dependent glucose transporter 2 inhibitors (SGLT2is), and mineralocorticoid receptor antagonists (MRAs), unless contraindicated or not tolerated.[3] Beyond pharmacological options, several device-based therapies have been explored. For instance, MitraClip catheter-based therapy has shown promise in improving outcomes for patients with secondary mitral valve insufficiency.[4] Given these constraints and the frequent co-morbidity of atrial fibrillation (AF) in HFrEF patients, alternative rhythm control strategies are crucial. Specifically, catheter ablation (CA) for AF has received a class I indication, following randomized trials that showed its beneficial effects on arrhythmic burden, HF symptoms, and mortality.[5] Implantable cardioverter defibrillators (ICDs) and cardiac resynchronization therapy (CRT) also contribute to the management of HFrEF.[3] While CRT offers benefits for some HFrEF patients, its applicability is limited: It is suitable for only approximately one-third of HF patients due to strict indications and contraindications. Moreover, approximately 30–40% of those receiving CRT do not experience significant improvements.[6] It is worth noting that for CRT non-responders with wide QRS, conduction system pacing (CSP), encompassing His bundle and left bundle branch pacing, has gained attention as an alternative method for resynchronization. Many electrophysiologists are considering CSP as a first-line approach in such scenarios.[7]

Against this backdrop of existing but limited therapies, cardiac contractility modulation (CCM) has emerged as a promising alternative. This is particularly true for individuals with a lower (25–45%) left ventricular ejection fraction and a QRS duration of less than 130 ms.[8] Numerous randomized trials have shown that CCM can improve a patient's quality of life, functional capacity, and HF symptoms and reduce the

frequency of HF hospitalizations.[8] Moreover, some research indicates a statistically significant positive effect of the use of CCM in patients with CHF and AF on LV FV, the functional class of CHF, and levels of NT-proBNP regardless of the aetiology of CHF.[9]

To better understand the precise therapeutic role of CCM, we conducted a systematic review examining its mechanism, factors that influence its effectiveness, its relationship with other cardiac implantable devices, potential drawbacks, and future prospects for this therapeutic approach.

Cardiac contractility modulation

Heart hypertrophy, caused by long-term hypertension or post-acute myocardial infarction in humans, can lead to decompensated failure as the hypertrophied segment consumes more energy, causing increased cell injury and death.[11] During overload, cardiac myocytes mechanically stretch, activating hypertrophic signalling pathways, reusing embryonic transcription factors, and increasing protein synthesis.[12] This results in hypertrophy responses, increased oxygen demand, and stimulation of myocardial angiogenesis to resolve hypoxic situations and maintain cardiac contractility. Cardiac myocytes and microvasculature interact, and repeated pathological overload leads to heart remodelling and maladaptation, ultimately causing HF.[12] Cardiac contractility modulation mechanisms include transient intracellular Ca^{2+} and myofilament responses.[10]

Mechanism of action

A CCM system typically consists of a charging device, a CCM pulse generator, and three leads. The efficacy and safety of CCM in the study could be similar when the signal was delivered through either one or two ventricular leads, which supported the potential use of a single ventricular lead for delivery of CCM.[13] The RV lead tips should be placed along the septal wall at least 2 cm apart, and proper placement is best appreciated if multiple oblique views are used; the proposed target zone is the septo-parietal trabeculations in the inferior portion of the septal right ventricular outflow tract (RVOT).[14]

CCM applies electrical signals during the absolute myocardial refractory period (ARP) to the right ventricle (RV) septal wall using a relatively high voltage, approximately 7.5 V, with a duration of approximately 20 ms and biphasic electric signals as a device-based therapy for HF patients.[15] Signal voltages can be set between 4.0 and 7.5 V, depending on patient tolerance, and four pulse duration phases can be selected, ranging from 5.14 to 6.60 ms, collectively lasting between 20.5 and 22.5 μs, with two biphasic pulses included in the stimulation train.[16] High-amplitude signals in the left ventricle (LV) during ARP could improve quality of life and exercise endurance.[17]

Biochemically, CCM uses an implantable impulse generator to send signals that increase inotropy by enhancing calcium influx into cardiomyocytes, prolonging the action potential. In the ARP, CCM impulses are delivered to the RV to improve ventricular contractile function.[18] The use of voltage clamps can alter the contractility of the heart by affecting the duration and amplitude of the action potential. In addition, isolated muscle strips (non-excitable currents, NEC) can improve the entry of calcium.[19] This mechanism goes beyond the traditional pharmacological effects of inotropic agents.[20] This theory is supported by experiments showing that LV function improved in both experimentally induced HF patients and dogs when electrical signals were applied to their failing myocardium.[21] Unlike cAMP-dependent positive inotropic drugs, CCM therapy improves LV function without significantly increasing myocardial oxygen consumption (MVO_2).[21] CCM modulates cardiac muscle contractions rather than rhythm, distinguishing it from pacemakers or defibrillators.[16] The primary mechanism of CCM in treating HF is shown in *Figure 1*.

Implantation procedure

The implantation of a CCM unit is in many ways similar to that of other cardiac implantable electrical devices (ICDs and pacemakers), which is best performed under moderate sedation in an OR grade sterile environment with fluoroscopic guidance; for most patients, there is an ICD already present in the left prepectoral area; therefore, most implants would be performed via contralateral right-sided access.[14] The CCM implant procedure was performed under local anaesthesia. After the preparation and sterile isolation of the right precordial region of the chest (the right subclavian area), two active fixation leads were advanced via the right subclavian vein into the RV and secured to the right ventricular septum; for each lead, mapping for an ideal position was performed before lead fixation to provide likely anatomical stability and effective delivery of CCM therapy.[16] RV lead tips were placed along the septal wall at least 2–3 cm apart and at least 3 cm apart from the defibrillation RV lead, and the target zone was the septo-parietal trabeculations in the inferior portion of the septal RV outflow tract.[16] The impulses enhance cardiac strength by triggering physiological processes in cardiac muscle cells. The CCM device was activated shortly after implantation.

Enhanced myocardial expression

The interactions between thick and thin filaments (α-actin, α-tropomyosin, and the troponin complex) during cardiac contractions are mediated by the myosin complex and myosin binding protein C.[23] When CCM signals are applied to failing hearts for 3 months, excitation-contraction coupling gene

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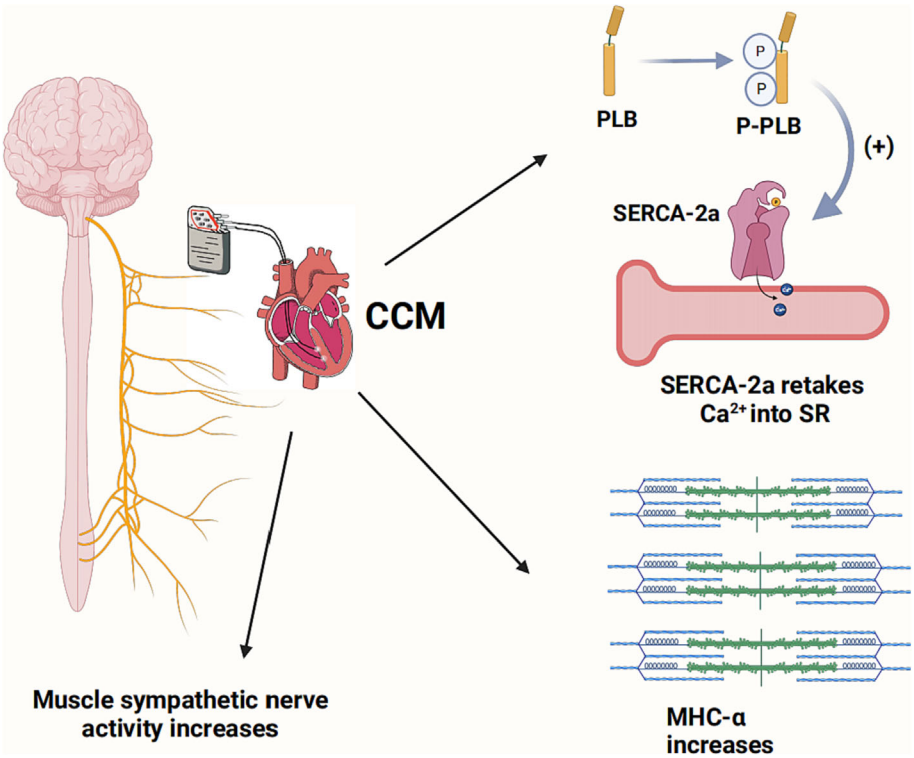
Figure 1 Primary mechanism of CCM in treating HF. CCM enhances cardiac contractility by up-regulating MHC-α expression, promoting intracellular calcium handling, and increasing sympathetic nerve activity in the muscles. CCM, cardiac contractility modulation; PLB, phospholamban; SERCA-2a, sarcoplasmic reticulum calcium ATPase; SR, sarcoplasmic reticulum.



expression improves, while genes related to myocardial stress decrease.[22] In a rabbit pacing tachycardia HF model, there were no differences in the mRNA levels of the alpha (1C)-subunit, Na^+/Ca^{2+} exchanger (NCX), and ryanodine receptor (RyR) between failing hearts and controls.[24] However, SERCA2a and phospholamban (PLB) mRNA levels were notably reduced.[24] In regard to protein levels, a significant increase in NCX protein, an unaltered outcome of alpha(1C) protein levels, and an apparent decrease in RyR, SERCA2a, and PLB were observed.[24] These findings suggest that the sarcoplasmic reticulum (SR) plays a crucial role in HF pathogenesis, with abnormal SR Ca^{2+} uptake and release causing altered Ca_i^{2+} and action potential profiles.[24] CCM signal therapy leads to beneficial molecular reverse remodelling, normalizing Ca^{2+} cycling in the sarcoplasmic reticulum and gene expression related to the stretch response.[22] After CCM therapy, down-regulated α isoform MHC expression in HFrEF patients reversed after 3 months, and phosphorylation levels of TnI and myosin-binding protein C increased in both LVs and RVs after 30 minutes of CCM signal delivery, continuing for 3 months (*Figure* 2).[23]

Autonomic nervous system

CCM treatment can precisely decrease muscle sympathetic nerve activity (MSNA) in HFrEF patients over several months.[23] Sympathetic stimulation increases cardiac output, myocardial work, and MVO_2, while parasympathetic stimulation lowers heart rate to enhance cardiac efficiency, reduces MVO_2, and lengthens coronary diastolic perfusion times without significantly affecting cardiac output.[25] Vagal stimulation can inhibit the positive chronotropic effects of sympathetic stimulation, as it has a dominant impact on heart rate.[25] Ultimately, CCM signals are expected to improve autonomic balance by reducing excess sympathetic activation associated with HF.[23]

Intracellular calcium metabolism

The versatile CaMKII is a calcium/calmodulin-dependent protein that can affect various aspects of the heart's function, such as promoting gene transcription and modulating inflammatory and proliferation responses.[26] It can work in combination with the sarcophagic reticulum's Ca^{2+} release channel ryanodine receptor 2 (RyR2) or independently to regulate the handling of this substance. Studies have shown that the presence of both CaMKII and sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase 2a (SERCA2a) leads to cardiac dysfunction in vivo.[26] The former is carried out through the reabsorption of Ca^{2+} by cardiomyocytes, while the latter is carried out through the sarcoplasmic/endurace reticulum.[28]

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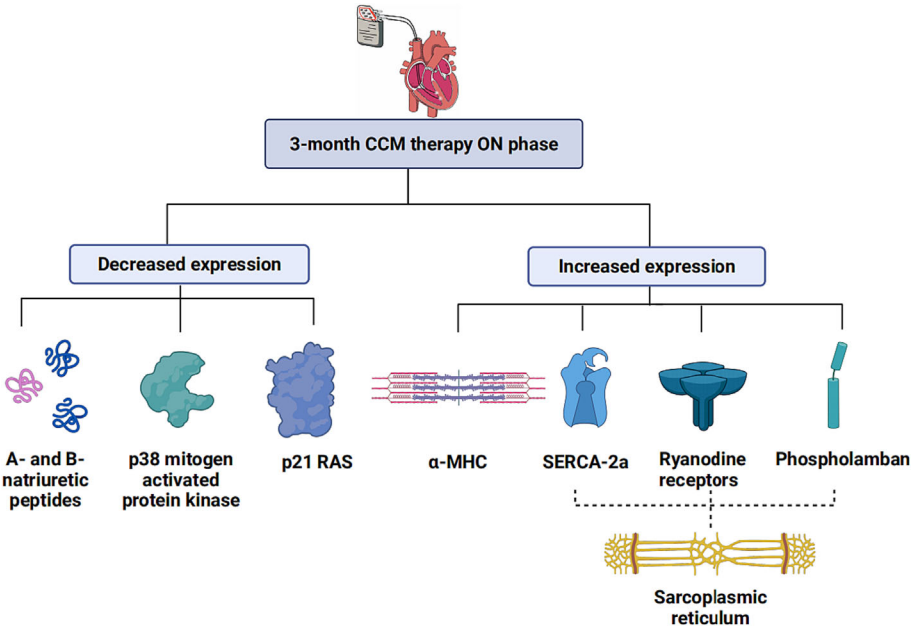
Figure 2 Main changes after 3 months of CCM therapy.



A multilevel signalling cascade regulates SERCA2a activity, involving phospholamban, protein phosphatase 1, inhibitor-1, PKCα, and post-translational modifications such as SUMOylation and acetylation.[27] Another study observed enhanced phosphorylation of phospholamban (PLB) within 2 h of applying CCM signals in dogs with heart failure (HF) symptoms as an acute effect.[28] When phosphorylated PLB is present, it can enhance the activity of SERCA-2a and its affinity for calcium. This can also increase the SR's capacity to carry out calcium cycling and contractility.[28]

Chronic CCM therapy can normalize the expression of the S100A1 protein, which is a Ca^{2+}-binding protein.[23] It interacts with other related proteins, such as RyR2, SERCA2a, and the cardiac titin complex. In patients with end-stage heart failure, the lower ejection fraction of their heart myocytes can reduce the number of S100A1 cells.[23] In mice with diseased hearts, S100A1 protein down-regulation contributes to contractile dysfunction, but in rat models of HF, myocardial contractile failure can be restored by transferring S100A1.[23]

Influencing factors

Sarcoplasmic reticulum

Impaired Ca transport and release in the sarcoplasmic reticulum (SR) are hallmarks of human and experimental heart failure, characterized by depressed SR calcium cycling.[31] When CCM impulses are given, extra calcium enters the cell through the SR, increasing calcium release from the sarcoplasm during the following systole, similar to the role of the SR in the voltage clamp technique. Strong contractions occur without CCM signals, while weak contractions occur with CCM signals.[19]

Adrenergic beta receptor blocker

The beta-adrenergic system mediates part of the CCM stimulation inotropic effect.[32] The positive inotropic influences of β-adrenergic agonists on the heart are mediated by inducing protein kinase-A (PKA) activation through β-adrenergic stimulation.[33] This effect increases Ca^{2+} influx through L-type $Ca_V1.2$ channels in cardiomyocytes, and PKA is believed to increase $Ca_V1.2$ currents by phosphorylating $Ca_V1.2$ α_{1C} and/or β_{2B} subunits. Multiple Ser/Thr residues on α_{1C} and β_{2B} may be phosphorylated by PKA to modulate $Ca_V1.2$ in cardiomyocytes.[33] For patients with heart failure, rosuvastatin can act as a mimic of the effects of adrenergic receptor antagonists by affecting the AC-cAMP-PKA pathway.[34] Part of this mechanism is illustrated in *Figure 3*.

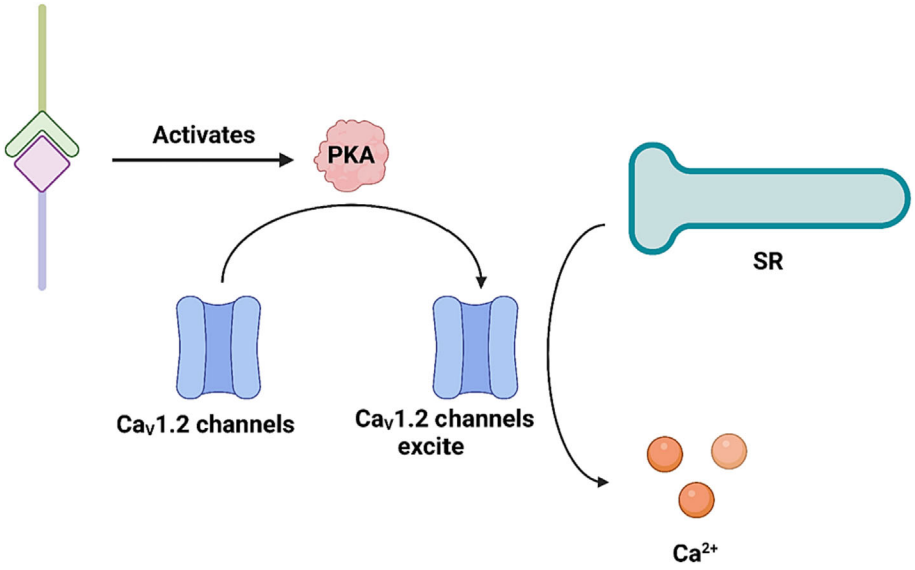
L-type calcium channels

Membrane depolarization during the action potential activates L-type $Ca_V1.2$ channels (LTCCs), which then release Ca^{2+} from the SR and increase the initiation of contraction in ventricular myocytes.[35] Blocking L-type calcium channels can blunt the effects of CCM signalling.[19] Part of this mechanism is illustrated in *Figure 3*.

Septal myocardial scar burden prediction

To predict CCM treatment responses at sites where CCM leads are placed, late gadolinium enhancement (LGE) using cardiac magnetic resonance (CMR) can be used to assess myocardial septal scarring.[36] Before implanting CCM in patients with HF who meet the criteria, LGE CMR imaging is ap-

Figure 3 Main mechanism of factors affecting CCM. CCM, cardiac contractility modulation; SR, sarcoplasmic reticulum; PKA, protein kinase A. Ca^{2+} can be released by SR, which can be promoted by activated $Ca_V1.2$ channels; PKA can excite $Ca_V1.2$ channels after the action of adrenaline on beta receptors.



plied. Variations in New York Heart Association (NYHA) class and echocardiographic assessments of left ventricular ejection fraction (LVEF) can confirm responses to CCM treatment during follow-up. This study demonstrates that CMR-LGE can predict CCM therapy responses by assessing septal myocardial scar burden at the lead position.[36] In myocardial segments with CMR-LGE burden <25% where leads are placed, an improvement in NYHA class can be observed.[36]

The impact of baseline left ventricular ejection fraction on long-term outcomes

CCM therapy can improve NYHA class and other clinical parameters regardless of baseline LVEF; for patients with LVEF values <30% before implantation, the potential for biventricular systolic recovery may improve over the long term after CCM therapy.[37]

Applications: Patient characteristics for cardiac contractility modulation use

Initially, designed for treating patients with sinus rhythm and narrow QRS, CCM has expanded its applications to include those suffering from atrial fibrillation (AF) and patients with wide QRS that do not respond to CRT.[16] Patients can be considered for CCM therapy if they meet the following criteria: (a) ejection fraction (EF) between 25% and 45%; (b) QRS duration less than 130 ms, ; (c) New York Heart Association (NYHA) class 3 or 4; and (d) history of HF treated with stable medications for at least 90 days.[30] However, patients with significant valvular disease, permanent or persistent AF, use of a biventricular pacemaker, QRS duration exceeding 130 ms, or those undergoing palliative treatment are not suitable candidates for CCM therapy.[30] CCM has proven to be safe and effective for patients with a narrow QRS (approximately 130 ms), EF between 25% and 45%, and moderate-to-severe symptomatic HF with EF of 25–45%.[29] Additionally, recent case studies suggest that CCM may benefit patients with AF and wide QRS (>130 ms).[29]

Effects and use status

CCM has been shown to positively impact various proteins and clinical parameters in chronic heart failure (CHF) animal models and human studies.[32,33] Partial restoration of Kv4.3, KCNQ1, KCNH2 and connexin 43 protein levels was observed after CCM therapy.[38] By down-regulating CTGF and Gal-3 and up-regulating Kv4.3, KCNQ1, KCNH2, and Cx43 by CCM, the heart may benefit from this therapy.[38] Long-term CCM therapy has been proven to be safe and effective, without causing adverse effects or changes in QRS duration.[40] A study conducted on 174 patients with CHF showed that the use of CCM significantly improved the left ventricular ejection rate and tricuspid aortic plane systolic excursion (TAPSE) after 3 and 5 years, respectively,[42] in non-ischaemic patients. CCM therapy has also been suggested as a potential bridge to transplantation in end-stage HFrEF patients who are not eligible for left ventricular assist systems (LVADs).[44] The Optimizer system, a CCM device, is now commercially available and approved for use in much of Europe,[43] and ongoing clinical trials in the United States are investigating its effects on

Table 1 Effects of CCM on HFrEF patients

	Effects on HFrEF patients of CCM
The intensity of LV contraction	↑
Intracellular calcium metabolism	↑
Ca^{2+} binding protein S100A1	↑
MLHFQ score	↑
LVEF	↑
Peak oxygen consumption	↑
New York Heart Association class	↑
MLWHFQ score	↑
TAPSE	↑
MHCα	↑
Levels of Kv4.3, KCNQ1, KCNH2 and connexin 43	↑
Myocardial fibrosis and hydroxyproline content	↓
MSNA	↓

HF mortality and morbidity.[43] Recently, there was a prospective registry that was designed to identify the subsets of patients who benefited more from CCM and to analyse how CCM affects those clinical outcomes in the long term.[41] An overview of the effects of CCM on HFrEF patients can be found in *Table 1*.

Analysis of effectiveness

Recent meta-analyses and clinical trials have demonstrated that while CCM may not be associated with reduced cardiovascular adverse events, it does result in significant improvements in cardiopulmonary function and capacity, making it a potential alternative treatment for advanced HF patients.[39,42,45,46] Some studies have observed improvements in quality of life and functional status[47] but no significant differences in 6-minute walk distance, arrhythmic events, hospitalizations, or mortality.[48] Further large-scale randomized controlled trials are needed to confirm the long-term benefits of CCM therapy.[33,40,41] Although tricuspid regurgitation (TR) is a potential complication of CCM device implantation, recent evaluations suggest that it does not worsen after the implantation of right ventricular electrodes for CCM therapy.[49]

Patient education and self-care advice

Patients should be thoroughly informed about the benefits, expectations, and potential complications of implanted devices, both in writing and verbally. They should also be educated about the indications, importance, and expectations for device check-ups, as well as any necessary follow-up methods, such as remote monitoring.[3] Knowledge of common complications and appropriate actions to take in response to them is essential for patients to manage their condition effectively.[3]

Relationship with other implantable equipment

Cardiac resynchronization therapy

CRT is a widely used therapy for treating heart failure patients with reduced ejection fraction and wide QRS complexes.[50] However, 20–30% of patients with HF and asynchrony do not respond to CRT; for these non-responsive patients, CCM can be used as an adjunctive treatment.[51] CCM therapy can help improve the quality of life for patients with reduced EF and moderate to severe HF symptoms.[52] Similar to CCM, CRT uses non-excitatory electrical stimulation during the absolute refractory period to improve ventricular contractile function without triggering extra systolic contractions.[53]

Implantable cardioverter-defibrillators

Implantable cardioverter-defibrillators (ICDs) can prevent bradycardia, correct potentially lethal ventricular arrhythmic events, and reduce the sudden arrhythmic death rate in patients with HFrEF.[53] One analysis showed a 27% reduction in all-cause mortality when ICD-only therapy was used in certain patients without a previous cardiac arrest.[54] For patients with HFrEF and a QRS duration greater than 130 ms, CRT-D is recommended instead of ICDs.[3] Currently, CCM systems have not shown interactions with transvenous or subcutaneous ICD devices, although randomized trials are lacking.[55] Many patients referred for CCM implantation with an LVEF below 35% may be suitable candidates for ICD implantation.[56] Recent developments in the United States have witnessed the first successful implantations of devices that combine ICD and CCM functionalities. Moreover, a study showed that the implantation of RV electrodes for CCM therapy did not worsen tricuspid regurgitation in HFrEF patients with ICD.[49]

Combined utilization with S-ICD

For patients with LVEF ≤35%, ICDs are indicated, and subcutaneous ICDs (S-ICDs) may also be prescribed. The combination of CCM and S-ICD in HFrEF patients can be successful without affecting the function of either device.[57] During the implantation of CCM or S-ICD as the second device, intraoperative crosstalk testing should be performed to prevent double counting.[57] Moreover, it is feasible to safely and effectively combine S-ICD with CCM in patients without cardiac pacing who have HFrEF.[57] However, significant bradycardia must be avoided, as neither device has pacing capabilities.[57] For HFrEF patients who require ventricular pacing or have a wide QRS complex, CRT is needed.[57] Currently, CCM and ICD functions cannot be combined in a single device due to

potential adverse events caused by the lead and implantation.[57] Further multicentre studies are needed to investigate the benefits of combining these two technologies for patients with HFrEF and LVEF below 35%.[57] In conclusion, combined S-ICD and CCM therapy is safe with long-term follow-up, and a device that combines ICD and CCM functions would ideally reduce risks by decreasing the number of intracardiac leads implanted in the future.[57] A recent case report has also illuminated that simultaneous implantation of CCM and S-ICD could significantly improve the clinical symptoms of patients with advanced HF in a single surgery, representing a promising avenue for future research and clinical practice.[58]

Conduction system pacing

Conduction system pacing (His bundle pacing and left bundle branch pacing) is a more physiologic method of pacing and avoids the deleterious consequences associated with long-term right ventricular pacing.[59] It can correct ventricular dyssynchrony in some patients, and more data are emerging on the potential benefit of CSP for CRT.[60] In addition, CSP improved clinical outcomes compared with biventricular pacing (BVP) in this large cohort of patients with indications for CRT.[61] His bundle pacing (HBP), alone or in conjunction with coronary sinus pacing, is a promising novel technique for delivering CRT that is useful in AF patients undergoing AVJ ablation.[62]

Related clinical studies

FIX-HF-3 clinical study

Although the underlying cellular mechanisms of CCM remain unclear, this study suggests that non-excitatory cardiac stimulation may significantly improve the clinical condition and systolic ventricular function in patients with drug-refractory CHF. However, further studies are required to define the underlying mechanisms and establish its most effective applications.[63]

FIX-HF-4 study

This randomized, double-blind, crossover study found CCM to be safe for patients with HF and LV dysfunction. Patients who received active CCM for 3 months experienced significant improvements in exercise tolerance, quality of life, and safety.[64] The OPTIMIZER System represents an innovative treatment modality for HF, and this study serves as a pivotal step in evaluating its efficacy.[64]

FIX-HF-5 study

This randomized trial, which was conducted to evaluate the effects of CCM on advanced HF patients, revealed that the procedure did not improve the patients' primary endpoint anaerobic ventilation threshold. However, it did improve pVO_2 and MLWHFQ in the overall target population, without adverse effects on hospitalizations or mortality.[65] Further studies are needed to analyse the various advantages of CCM for patients with refractory symptoms of HF.[65]

FIX-HF-5C study

The FIX-HF-5C trial compared the previous three-lead system with the two-lead Optimizer device, demonstrating similar safety and efficacy profiles.[66] This study also found that CCM reduced NYHA class III symptoms in patients with mild–moderate LV dysfunction (EF 25–45%).[66] CCM has consistently shown improvements in peak VO_2, 6MWD, and NYHA functional class in various studies, suggesting that it mitigates HF symptoms without increasing myocardial oxygen consumption and reduces hospitalizations.[66] Future research will concentrate on integrating CCM into HFpEF patients requiring obligatory ventricular pacing and those with atrial arrhythmias.[66]

FIX-HF-5C2 study

The researchers then analysed the data collected during the trial to determine the subgroup of participants who responded to the CCM. They discovered that the exercise tolerance in the group that responded to the procedure improved significantly.[67]

FIX-HF-5 C^{18} study

The goal of the study was to confirm the findings of an analysis of patients with EFs between 25% and 45% in the previous FIX-HF-5 trial. This suggests that CCM improves exercise tolerance and quality of life when prescribed for patients with persistent NYHA functional class III or ambulatory class IV symptoms. A post hoc analysis revealed that the CCM procedure significantly decreased the hospitalization rate and cardiovascular death rates.[68]

Feasibility study of advanced HF in patients with normal QRS duration

While the sample size of this trial was too small to achieve statistical significance, preliminary results indicated potential improvements in exercise tolerance, pVO_2, and anaerobic

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threshold in the experimental group. Further research is needed to definitively establish the safety and efficacy of CCM.[69]

Multicentre study of primary CCM for systolic HF

Although CCM therapy appears to be without an impact of proarrhythmic effects, it has shown promising results as a safe and feasible treatment option for systolic heart failure. Preliminary evidence indicates gradual and substantial improvements in systolic performance, symptoms, and functional status.[70] This study underlines the importance of controlled, randomized trials to validate CCM as an additional treatment for severe heart failure.

CCM's impact on remodelling and LV function at global and regional levels

Using 3D echocardiography and tissue Doppler imaging, researchers found that CCM effectively improved both global and regional contractility of the left ventricle (LV), including remote zones without impulse delivery.[71] This suggests a potential for enhancing LV reverse remodelling and systolic function. Notably, these improvements were not attributable to changes in diastolic function or mechanical dyssynchrony.[71]

Empirical study of CCM in CHF patients

Preliminary findings indicate that intermittent non-excitatory electrical stimulation via CCM may benefit drug-resistant NYHA class III heart failure patients by improving their symptoms and ventricular function.[63] After CCM therapy, patients experienced improvements in ejection fraction, NT-proBNP levels, exercise capacity, NYHA class, and quality of life, resulting in lower mortality rates than estimated by the MAGGIC score.[72]

A randomized comparison of two-ventricular versus one-ventricular leads

This study found that CCM delivery was equally effective and safe when using one or two ventricular leads.[13] As a result, CCM can be administered with a single ventricular lead according to these findings.

CCM's effects on HF patients with mild systolic dysfunction

Preliminary results suggest that the exercise tolerance and quality of life of patients with an LVEF between 40 and 45% could be improved with CCM.[73] Further randomized controlled studies are needed to confirm these effects.

Chronic CCM use and its clinical effect on heart failure patients with LV systolic dysfunction

CCM therapy provides safe and effective long-term symptom and functional improvement for heart failure patients.[74] These benefits are unrelated to baseline LVEF levels, and the safety profile is consistent with published device trials.[74]

Randomized comparison of effects in heart failure patients treated with 5 or 12 h of CCM therapy

CCM therapy appears to be equally safe and effective when applied for short (5 hours) or long (12 hours) daily periods.[75] However, more research with larger sample sizes is still needed to confirm these findings (*Table* 2).

Application prospects and disadvantages

Despite its potential, CCM therapy still has some limitations. Currently, there is no concrete evidence that CCM reduces mortality or hospitalization rates for heart failure patients.[18] Additionally, electrophysiologists and device clinic staff will need training in the implantation, analysis, evaluation, and optimization of CCM devices.[29] However, due to similarities between ICD and CRT implantation techniques, implementation progress and infrastructure development could be relatively straightforward.[29] The advent of devices that integrate ICD and CCM functionalities offers a more holistic approach to patient management and is a promising area for ongoing research.

Although the effects of CCM on various conditions have been acknowledged, further studies are needed to analyse the exact effects of the procedure on the different patient groups. For instance, no studies have been conducted on the effects of the procedure on the development of right ventricular failure and diastolic hypertension.[29] These patient populations should not be overlooked in future CCM research.

Moreover, the follow-up time for CCM treatment effects has been relatively short, and there is a lack of randomized

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Table 2 Clinical trials of CCM therapy for HF

Studies	Type	Types of patients	The number of patients	Content	If reached the endpoints
Feasibility study for advanced HF in patients with QRS durations within normal ranges	Randomized, double-blind, pilot study	EF < 35%, normal QRS duration, and NYHA class III or IV HF	49	pVO_2, 6MWD, anaerobic threshold	Yes
FIX-HF-3	-	drug-refractory NYHA class III HF	25	LVEF, MLWHFQ	Yes
FIX-HF-4	Randomized, double blind, crossover study	EF < 35% with NYHA II or III	164	pVO_2, MLWHFQ	Yes
FIX-HF-5	Prospective, randomized, parallel group, controlled trial	optimal medical therapy (OMT) + CCM or OMT only	428	pVO_2, MLWHFQ	Yes
FIX-HF-5C	Retrospective hypothesis-generating analysis	97 for OMT and 109 for CCM	206	pVO_2, MLWHFQ	Yes
FIX-HF-5C2	Randomized, controlled	NYHA functional class III or IV HF, EF ≥ 25% and ≤45%, and QRS < 130 ms	160	pVO_2, 6MWD, MLWHFQ	No
FIX-HF-5 C[18]	Prospective, randomized, multicentre study	NYHA III and IV, EF is between 25% and 45%	160	Difference of pVO_2	Yes
Clinical effects of CCM in HF with mildly reduced systolic function	Randomized, controlled, blinding	Range of LVEF is between 40% and 45%	53	pVO_2, 6MWD, MLWHFQ	Yes
Randomized comparison of signal delivery through one vs. two ventricular leads	Prospective blinded randomized trial	LVEF<40%, pVO_2 ≥ 9 mL O_2/kg/min	48	NYHA, MLWHFQ	Yes
CCM effects in patients with HF caused by LV systolic dysfunction after long-term CCM administration	Followed via clinical registry for 24 months	HF patients with LVEF<35% or LVEF≥35%	143	NYHA, MLWHFQ, 6MWD, LVEF, pVO_2	Yes
HF patients' response to 5 versus 12 hours of CCM treatment	Randomized controlled trial	HF and reduced LV function who underwent implantation of an Optimizer™ system	19	NYHA, MLWHFQ, 6MWD, LVEF, pVO_2	Yes
Global and regional impacts of CCM on LV operations and remodelling	-	NYHA functional class III HF, EF < 35%, and QRS < 120 ms	30	NYHA, 6MWD	Yes

control groups. Studies on combination therapies and long-term use are also limited. The relationship between atrial fibrillation burden and CCM device implantation has not been explored, necessitating further investigation.[76] Future studies could improve treatment outcomes and expand the beneficiary population by combining CCM with multiple treatment regimens.

Conclusions

In summary, CCM primarily aims to treat heart failure by enhancing myocardial function, targeting CRT-non-responsive patients with a wide QRS duration. Factors such as the sarcoplasmic reticulum, β receptors, and L-type calcium channels can influence CCM's effectiveness. As larger samples and diverse populations are studied, the therapeutic effects and application scope of myocardial contractility regulators will become increasingly clear.

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Conflict of interest

The authors have nothing to disclose.

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