Cardiac contractility modulation therapy in advanced systolic heart failure

Alexander R. Lyon, Michael A. Samara and David S. Feldman

Abstract | Cardiac contractility modulation (CCM) is the application of nonexcitatory electrical signals to the myocardium, during the absolute refractory period of the action potential, to elicit a positive inotropic effect without increasing myocardial oxygen consumption. These effects are independent of QRS duration; consequently, CCM device therapy might benefit symptomatic patients with reduced left ventricular ejection fraction who are not candidates for cardiac resynchronization therapy. Preclinical studies have demonstrated a rapid positive inotropic effect of CCM, which seems to be mediated by modulation of cardiomyocyte Ca^{2+} fluxes and alterations in the phosphorylation of cardiac phospholamban. *In vivo* translational and clinical studies that utilized double biphasic voltage pulses to the right ventricular aspect of the interventricular septum have demonstrated positive global effects on cardiac reverse remodelling and contractility. Long-term application of CCM seems to improve patients' exercise tolerance and quality of life. These benefits are apparently accomplished with an acceptable safety profile; however, to date, no data have demonstrated reductions in hospitalizations for heart failure or mortality. CCM is currently available in Europe and ongoing studies are attempting to identify the ideal target population and accumulate additional outcome data.

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Introduction

With the exception of ivabradine,[1] physicians caring for patients with systolic heart failure have witnessed a drought lasting nearly 2 decades in the introduction of new pharmacological therapies. However, the same period has seen a revolution in the development of medical devices to treat heart failure, including cardiac resynchronization therapy (CRT) and ventricular assist devices (VADs), which offer options for patients who have persistent symptoms of heart failure despite optimal medical therapy. Although distinct in their mechanisms and target populations, both pharmacological and device therapies can improve patients' symptoms, quality of life, and survival by providing favourable effects on myocardial energetics and remodelling. Continued refinement of the target populations for these therapies has led to variably contracting and expanding candidacy pools. However, the majority of patients with heart failure are not candidates for either CRT or a VAD because they lack a prolonged QRS or have insufficiently severe symptoms. To treat such patients, investigators have turned to observations first made in the 1960s, which demonstrated that application of extracellular electrical stimulation to the myocardium during the absolute refractory period of the action potential leads to increased contractile strength and prolonged action potential duration.[2]

The precise molecular mechanisms underlying these effects of cardiac contractility modulation (CCM) are unknown, but the contractile effect seems to involve changes in cardiomyocyte Ca^{2+} fluxes, both across the sarcolemma and between the sarcoplasmic reticulum and cytoplasm. This conclusion arises from both the findings of experimental studies and from drawing parallels with other treatments for chronic heart failure that target the sarcoplasmic reticulum and can induce beneficial reverse remodelling in the heart. The chronic changes associated with CCM partly resemble the reverse remodelling induced in failing hearts by unloading with left VADs, CRT with biventricular pacemakers, or restoration of sarcoplasmic reticulum Ca^{2+} ATPase2a (SERCA2a) function by gene transfer.[3–6] Furthermore, the myocardial changes induced in failing hearts by chronic CCM therapy contrast with those observed during chronic treatment with pharmacological positive inotropes, such as dobutamine and milrinone, which lead to worse clinical outcomes.[7–10] This discrepancy suggests that CCM does not increase myocardial contractility via elevation in cyclic AMP levels (Box 1). This observation is important, given that treatment with dobutamine and milrinone is associated with impaired outcomes owing to pro-arrhythmic effects, accelerated metabolic compromise, and myocardial dysfunction.[7,8]

In the past 15 years, a series of experiments using various models have characterized the alterations in cardiac physiology that accompany this type of electrical stimulation. This stimulation, and the resultant potentiation of systole (myocardial contraction), has been termed CCM. The preclinical evidence clearly shows that CCM application to cardiac muscle preparations or intact hearts, both *in vivo* and *ex vivo*, stimulates a positive

Competing interests
The authors declare no competing interests.

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Key points

- Cardiac contractility modulation (CCM) is the application of nonexcitatory electrical signals to the myocardium, during the absolute refractory period of the action potential, to augment contraction without increasing oxygen consumption
- Preclinical studies evolved from using high-amplitude monophasic current pulses to using double-biphasic voltage pulses; the latter have been used in all clinical trials
- The mechanisms underpinning the effects of CCM are still unclear but might be partly mediated by alterations in myocyte Ca^{2+} transients and cardiac phospholamban phosphorylation
- In patients with NYHA class III–IV heart failure, CCM improves reverse remodelling and contractility, independent of QRS duration; these benefits are additive to those of cardiac resynchronization therapy (CRT)
- CCM improves peak oxygen consumption and quality of life, and these benefits are of a comparable magnitude to those achieved using cardiac resynchronization therapy in patients with prolonged QRS duration
- Ongoing studies of CCM are generating clinical outcome data and aim to identify the ideal target population for this therapy

Box 1 | Evidence for a cAMP-independent mechanism of CCM*

- The application of positively charged CCM current pulses increases the force of paced contractions, and this increase begins immediately upon CCM stimulation
- A stepwise increase in positive CCM current amplitude, or duration of current pulse, correlates with increased force generation
- CCM increases action potential duration in a dose-dependent manner
- Negative charged CCM current pulses have a negative inotropic effect, inducing an acute reduction in force and action potential duration shortening
- Applying positive CCM current pulses to alternate paced beats induces a positive inotropic effect on subsequent non-CCM treated beats (that is, CCM has a greater effect on the subsequent heart beat compared with beats receiving the signal)
- Increasing ryanodine receptor opening probability using ryanodine has a mild negative inotropic effect at baseline via reduction in sarcoplasmic reticulum calcium load, but abolishes the positive inotropic effects of CCM
- Inhibition of β-adrenergic receptors with propranolol is negatively inotropic at baseline, but does not alter the effects of CCM, implying that CCM acts independently of both cardiac sympathetic nerve terminals, their norepinephrine release, and the β-adrenergic receptors themselves[70]

*Although these observations support the conclusion that the effects of monophasic CCM current pulses are independent of cAMP, direct measurement of cAMP during CCM, and use of cAMP agonists and antagonists in CCM studies, have not been performed to confirm this hypothesis. Abbreviation: CCM, cardiac contractility modulation.

inotropic effect on myocardial contraction. Moreover, CCM induces immediate and sustained improvements in left ventricular function in large-animal models of chronic heart failure. Consequently, investigators have started a translational and clinical trial programme to explore the efficacy of CCM in patients with chronic heart failure. However, the results from experimental studies and CCM clinical trials raise a number of key questions. Firstly, how do electrical CCM pulses in the absolute refractory period exert this positive inotropic effect at the cellular and molecular levels? Secondly, how do the effects of CCM manifest *in vivo* in the locally stimulated region of muscle in the intact heart? Finally, how can CCM applied to a specific myocardial region induce global reverse remodelling of the failing heart *in vivo*?

In this Review we describe the preclinical data and discuss potential mechanisms that might account for the beneficial effects of CCM in the failing heart. We also review the clinical evidence on the use of CCM, and debate whether it can be used in the routine management of patients with chronic heart failure.

CCM protocols

Over time, the nature and amplitude of the electrical pulses delivered during CCM therapy has evolved. Initial preclinical studies used high-amplitude, square wave, biphasic current pulses (± 20 mA), which were delivered over a 30–40 ms period after the initiation of ventricular pacing in *ex vivo* preparations of small rodent hearts and cardiac muscle (Figure 1a).[11] Subsequent studies in *ex vivo* rabbit hearts and failing human papillary muscles used either high-amplitude (± 20 mA), biphasic or low-amplitude (3–8 mA), monophasic current pulses of 20–40 ms duration to study the effect of CCM on cardiac sympathetic nerve activity.[12,13] The majority of existing mechanistic preclinical data was acquired using these two pulse protocols (high-amplitude, biphasic and low-amplitude, monophasic, respectively).

However, the clinical pulse protocol delivered by the Optimizer® II (Impulse Dynamics NV, Netherlands Antilles) device, which has been used in failing canine hearts *in vivo* and in clinical studies, is markedly different. This device delivers double biphasic voltage pulses (± 7.7 V) with a total pulse width of ~20 ms—that is, ~10 ms per pulse. Consequently, extrapolation from the mechanistic preclinical data to explain the CCM findings in clinical studies using the Optimizer® II device must be made with caution. Our review of the available data will, therefore, be divided into preclinical studies, applying the two experimental current pulse protocols, and clinical studies using the voltage pulse protocol.

Preclinical data

Ex vivo cardiac muscle preparations

A striking feature of the low-amplitude, monophasic current pulse CCM protocol is the immediacy of its effect on the contractility of isolated cardiac muscle preparations, in which it alters the contraction profile of the subsequent (intrinsic or remotely paced) contraction (Figure 1b,c). Contraction of *ex vivo* healthy rabbit papillary muscles mounted in an organ bath was measured via a force transducer during stimulation with and without low-amplitude, monophasic CCM current pulses of varying length and polarity.[12] A number of important mechanistic findings were reported in this study, which should be integrated when considering hypotheses to explain the molecular mechanism of CCM. These findings support the conclusion that the positive inotropic effect of low-amplitude monophasic CCM current pulses are independent of cAMP (Box 1), although direct measurement of cAMP levels has not been performed during CCM, and the effects of cAMP agonists and antagonists on CCM parameters have not been investigated to confirm this hypothesis. However, contradictory evidence exists regarding the effects of CCM on cardiac sympathetic nerve function in intact *ex vivo* hearts, discussed below.

Ex vivo intact hearts

Early CCM studies directly analysed Ca^{2+} transients from epicardial cardiomyocytes using the Ca^{2+}-sensitive dye aequorin.[11] This dye was used for optical mapping of Ca^{2+}

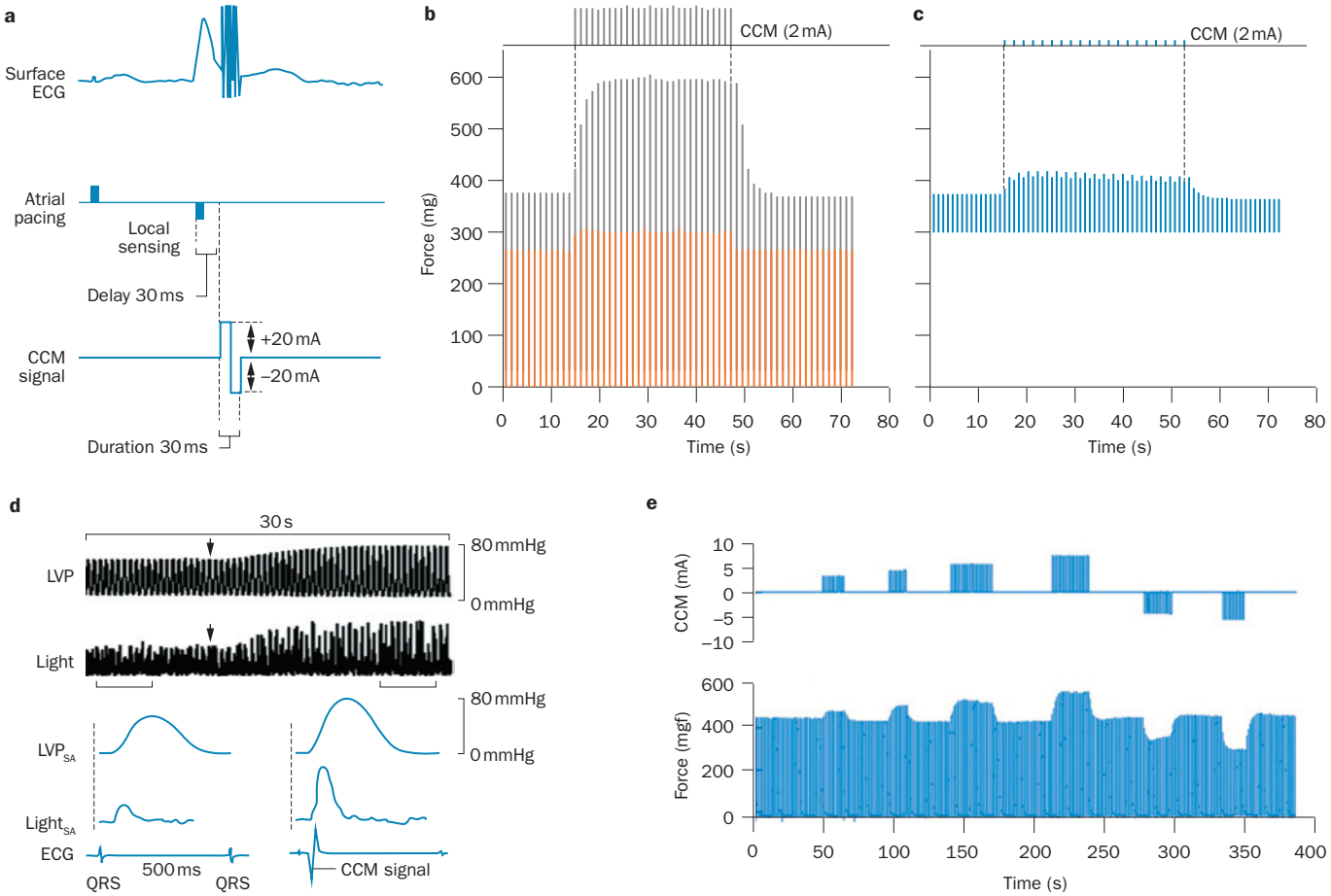

Figure 1 | The effect of experimental CCM protocols on myocardial function. **a** | Surface ECG showing a CCM pulse using the original experimental CCM protocol (a single biphasic ± 20 mA current pulse applied 20 ms after myocardial depolarization).[25] **b** | A 2 mA monophasic CCM current pulse in a rabbit papillary muscle preparation increases contractile force (grey trace) and is inhibited by ryanodine pretreatment (red trace).[12] **c** | Experimental CCM current pulses, to induce alternating stimulated contractions of *ex vivo* rabbit papillary muscle, initiate alternating enhancement of the contractile force in the subsequent stimulated contraction.[12] **d** | High-amplitude, biphasic current pulses in *ex vivo* ferret hearts (initiated at arrow) increase both left ventricular force and Ca^{2+} transient amplitude, measured by aequorin fluorescence. Signal averaged examples of LVP and fluorescence-emitted (Light) signals on traces below.[11] Aequorin signals from *ex vivo* ferret hearts before and after amplification of experimental CCM impulses. The calcium transients demonstrate increases in both peak amplitude and apparent rate of decay.[11] **e** | Increased duration or amplitude of monophasic CCM pulses initiate corresponding increases in papillary muscle contraction. Negative (cathode) charge current pulses reduce contraction.[12] Abbreviations: CCM, cardiac contractility modulation; ECG, electrocardiogram; LVP, left ventricular pressure; SA, signal averaged. Permission obtained for panel a from The American Physiological Society © Mohri *et al. Am. J. Physiol. Heart Circ. Physiol.* **282**, H1642–H1657 (2002).[25] Permission obtained for panels b, c and e from Oxford University Press © Brunckhorst *et al. Eur. J. Heart Fail.* **8**, 7–15 (2006). Permission obtained for panel d from The American Physiological Society © Mohri *et al. Am. J. Physiol. Heart Circ. Physiol.* **284**, H1119–H1123 (2003).[11]

signals in intact heart preparations in the early 1990s. High-amplitude (supraclinical) single biphasic CCM current pulses (± 20 mA) were applied to *ex vivo* ferret hearts injected with aequorin. These high-amplitude pulses increased the amplitude and decreased the time-to-peak values of recorded cytoplasmic Ca^{2+} transients, which correlated with the changes in cardiac contractile parameters measured with an intracavity pressure transducer. Increasing extracellular Ca^{2+} levels via the perfusate resulted in a dose-dependent, incremental increase in the CCM-stimulated Ca^{2+} transient amplitude, when a high-amplitude CCM current pulse was used. However, whereas the left ventricular developed pressure rose when this CCM protocol was used at physiological Ca^{2+} levels, it plateaued at supraphysiological Ca^{2+} levels, a finding that is consistent with saturation of either myofilament Ca^{2+} sensitivity or sarcoplasmic reticulum Ca^{2+} loading.

Increases in cytoplasmic Ca^{2+} transient amplitude could occur via a number of mechanisms in the sarcoplasmic reticulum. An important point to note is that these mechanisms are not necessarily mutually exclusive. Firstly, an increase in ryanodine receptor opening probability during systole might lead to an immediate increase in Ca^{2+} transient amplitude via one of three mechanisms: activation of additional ryanodine receptor clusters;

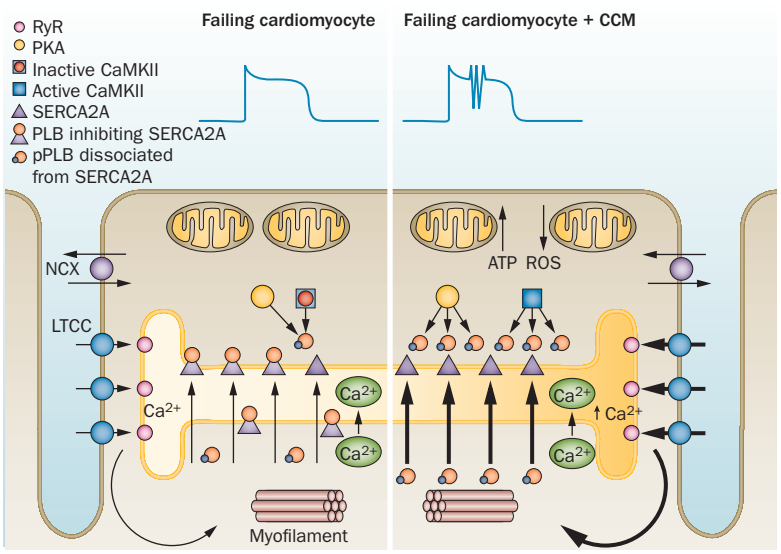

Figure 2 | Ca^{2+} cycling in the failing and CCM-treated cardiomyocyte, based on observations from preclinical studies of high-amplitude current pulses. In the failing cardiomyocyte (left), reduced LTCC-mediated Ca^{2+} entry, decreased sarcoplasmic reticulum Ca^{2+} load and release, severely impaired sarcoplasmic reticulum Ca^{2+} uptake, and enhanced Ca^{2+} clearance by sarcolemmal NCX, contribute to the phenotype. CCM therapy enhances LTCC-mediated Ca^{2+} entry, NCX mediated Ca^{2+} entry, PLB phosphorylation, and SERCA2 activity, contributing to enhanced efficiency of cytoplasmic–sarcoplasmic reticulum calcium transfer and increased contractile force (right). Abbreviations: CCM, cardiac contractility modulation; LTCC, L-type voltage-dependent Ca^{2+} channel; NCX, Na^+,Ca^{2+} exchanger 1; PKA, protein kinase A; PLB, cardiac phospholamban; ROS, reactive oxygen species; SERCA2A, sarcoplasmic reticulum Ca^{2+} ATPase.

increased duration or frequency of opening of individual ryanodine receptors; or increased conductivity.[14] However, the effect would need to be restricted to systole, because increased ryanodine receptor opening in diastole would reduce both the sarcoplasmic reticulum Ca^{2+} load and the Ca^{2+} transient amplitude, which are inconsistent with the observed effects of CCM.[15] The effect would also require memory lag to influence ryanodine receptor gating during systolic phase of the next stimulated beat.

Alternatively, increased trans-sarcolemmal Ca^{2+} influx via L-type Ca^{2+} channels (LTCCs) and/or Na^+-Ca^{2+} exchange protein 1 (NCX), in addition to Ca^{2+} influx into the sarcoplasmic reticulum via the cardiomyocyte Ca^{2+} pump SERCA2a (activity of which is regulated by the integral membrane protein, cardiac phospholamban; unphosphorylated phospholamban inhibits SERCA2a, whereas phosphorylation of phospholamban removes this inhibitory effect), might increase sarcoplasmic Ca^{2+} loading and, therefore, increase cytoplasmic Ca^{2+} transient amplitude.[16] CCM might increase LTCC opening or reactivation, during phase 2 of the action potential (that is during the absolute refractory period), to explain the positive inotropic effect of this intervention. LTCC opening would increase both cardiomyocyte Ca^{2+} influx and sarcoplasmic reticulum Ca^{2+} loading, resulting in prolongation of the action potential duration. However, this effect would be expected to immediately enhance contraction via systolic Ca^{2+} influx upon CCM application, that is from the initially modulated beat. Moreover, in the failing heart, LTCC reactivation and cardiomyocyte Ca^{2+} loading are associated with accelerated deterioration of heart failure and a poor clinical outcome, as well as with arrhythmogenic effects (including early and late after-depolarizations).[17,18] On balance, the beneficial findings of *in vivo* CCM studies, would suggest that LTCC reactivation is not the predominant mechanism underlying CCM, although further studies are required to clarify this.

Another possibility is that CCM causes a transient increase in Ca^{2+} influx via NCX. The direction of Ca^{2+} transport by NCX is voltage-dependent, and biphasic CCM pulses could conceivably initiate reverse transport of Ca^{2+} by NCX, increasing Ca^{2+} influx and leading to secondary Ca^{2+} loading of the sarcoplasmic reticulum. However, given the observations that reverse remodelling is induced by CCM (in the clinical studies described below), NCX-mediated Ca^{2+} influx alone does not seem to be the most plausible explanation, although it could still contribute to the effects of CCM in combination with a direct, sarcoplasmic-reticulum-dependent mechanism.

Increasing SERCA2a activity can also increase the sarcoplasmic reticulum Ca^{2+} load, which, in turn, increases the Ca^{2+} transient amplitude for the subsequent beat (as observed in CCM)[11] without prolonging the Ca^{2+} transient decay time.[19] However, one finding in these experiments that is inconsistent with observations made during CCM is the lack of an effect on relaxation of the myocardium.[11] Unfortunately, Ca^{2+} transient kinetics were not analysed in this study, but data displayed in the report suggested that the decay of Ca^{2+} transients was accelerated by high-amplitude CCM current pulses. If confirmed in other studies, this observation would be very important, because it would provide direct evidence that CCM increases the activity of SERCA2a. Additionally, molecular changes in CCM-treated failing hearts might further increase SERCA2a activity. In particular, the CCM-driven normalization of elevated diastolic Ca^{2+} levels in the failing heart might be associated with reductions in generation of reactive oxygen species (ROS) and activation of CaMKII, as critical factors to assure that the observed positive inotropy has beneficial, rather than detrimental, long-term effects.[20] A combination of increased LTCC Ca^{2+} current and increased SERCA2a activity (perhaps via relief of phospholamban-mediated inhibition) might be sufficient to explain the effects observed after CCM treatment (Figure 2).

Important post-translational modifications of SERCA2a in the failing heart have now been described, which reduce the activity of this protein.[21] The presence of dysfunctional SERCA2a, as observed in patients with advanced heart failure,[21] might plausibly limit the efficacy of CCM therapy if SERCA2a activity cannot be sufficiently increased. Conversely, in the early stages of heart failure development, when SERCA2a is still functionally active (despite its reduced expression), the residual amount of active protein might be sufficient to translate the stimulatory effects of CCM into a functionally relevant change in stimulated Ca^{2+} transients and cytoplasmic diastolic Ca^{2+} levels. This residual SERCA2a activity

might also explain why CCM is of increased benefit in patients with moderate heart failure (left ventricular ejection fraction [LVEF] 35–45%), although other factors might also be involved.

In other studies, CCM reduced left ventricular end-diastolic pressure in failing canine hearts, which might indirectly reflect improved ventricular compliance and relaxation, and improved diastolic Ca^{2+} physiology.[22] These preclinical findings (and similar observations in patients with chronic heart failure discussed below) suggest that changes in LTCC and sarcoplasmic reticulum Ca^{2+} physiology might underpin the acute inotropic effects observed with CCM, especially in the context of increased phospholamban phosphorylation.

The effect of high-amplitude, biphasic current pulses on cardiac function and electrophysiology has been further explored in *ex vivo* Langendorff-perfused healthy rabbit hearts.[13] The CCM pulses were delivered via epicardial electrodes, and the resulting intracavity pressures and epicardial monophasic action potentials were measured. These measurements provided three new insights that support a potential role for cardiac sympathetic nerve activation in CCM-mediated positive inotropy. Firstly, cardiac norepinephrine release in the coronary venous effluent increases in a dose-dependent manner (Figure 3a). Secondly, application of CCM to the basal and mid left ventricular epicardial surface has a significantly greater effect than its application to the apical myocardium (Figure 3b). Many physiological parameters in the mammalian heart exhibit gradients (which are highest at the base and decrease towards the apex) that could explain this effect, including sympathetic nerve density. Finally, pretreatment with the β-blocker metoprolol attenuated the CCM-induced inotropic responses (Figure 3c).

In this study, CCM also shortened the surface monophasic action potential, which is consistent with an increase in the I_{Ks} current mediated by β1 adrenergic receptors, but contrary to previous reports that CCM prolongs action potential durations. The researchers concluded that CCM triggers an inotropic response via cardiac sympathetic nerve activation and stimulation of norepinephrine release,[13] and noted that these observations correlated with the results of a previous study, in which electrical pulses were delivered in the absolute refractory period via a coronary sinus catheter, and increases in cardiac norepinephrine spillover were recorded.[23] These findings are also contrary to a previous report that found no effect of pretreatment with the β-blocker propranolol.[12] The differences between the results of these studies might relate to the different experimental models used, as *ex vivo* intact hearts have increased sympathetic nerve terminal density and residual capacity compared with papillary muscle preparations. Moreover, epicardial stimulation might affect an increased proportion of sympathetic nerves, which initially pass across the epicardial surface before entering deeper layers, compared with direct endocardial activation of papillary muscles. Norepinephrine-mediated activation of β1 adrenergic receptors might explain

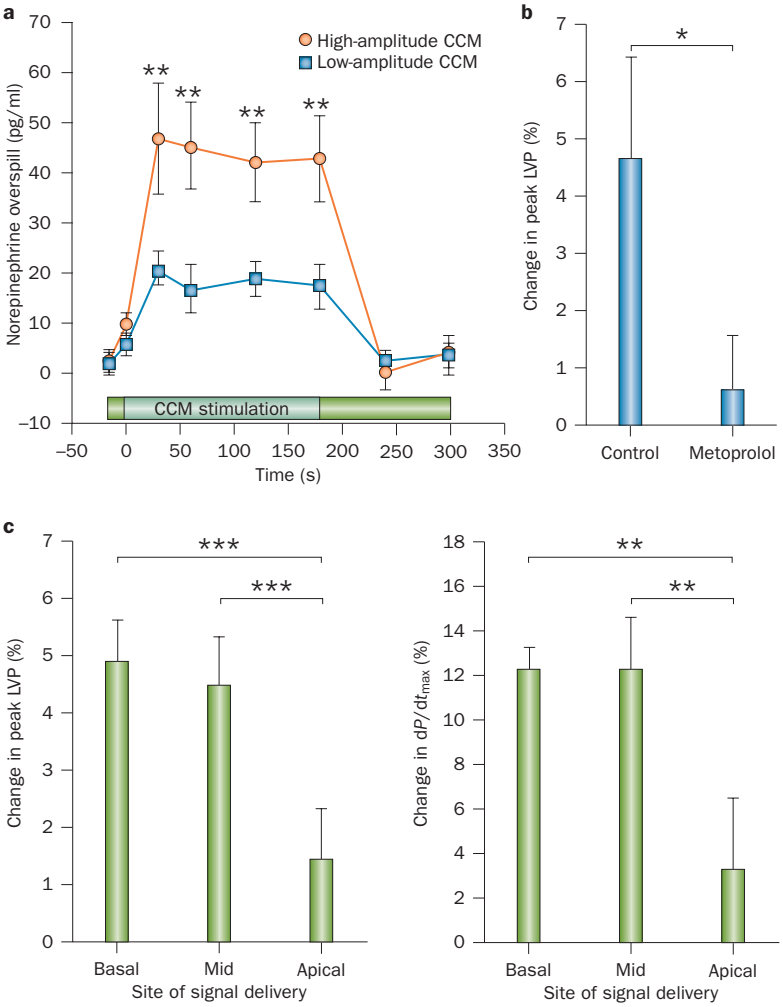

Figure 3 | The cardiac sympathetic nerve stimulation hypothesis for CCM-mediated positive inotropic effects. **a** | Cardiac norepinephrine overspill increases with CCM in a dose-dependent manner in *ex vivo* rabbit hearts. **b** | Pretreatment with the β-blocker metoprolol prevents CCM-mediated positive inotropic responses in isolated rabbit heart preparations. **c** | CCM application to basal and mid ventricular myocardium induces greater inotropic responses than CCM application to apical myocardium.[13] Abbreviations: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$; CCM, cardiac contractility modulation; LVP, left ventricular pressure. Permission obtained from Elsevier Ltd © Winter. J. *et al. J. Mol. Cell. Cardio.* **51**, 252–262 (2011).[13]

some, but not all, of the acute CCM-associated changes in contraction, Ca^{2+} transients, and regulation of the Ca^{2+} flux by phosphorylation of cardiac phospholamban (an integral membrane protein, the phosphorylation status of which regulates the Ca^{2+} pump, SERCA2a, in cardiomyocytes: unphosphorylated phospholamban inhibits SERCA2a, whereas phosphorylated phospholamban lacks this inhibitory effect), as discussed in more detail below. However, established evidence clearly shows that long-term β1 adrenergic receptor activation is maladaptive and deleterious in the failing heart. Moreover, the molecular and structural reverse remodelling, and the improvement in myocardial energetics observed both in humans and in animal models of heart failure, suggests that CCM is associated with alternative (or additional) mechanisms countering the adverse effect of sympathetic

nerve stimulation and β1 adrenergic receptor activation.[24] Furthermore, in both animal studies and human trials of CCM, the benefits of the treatment have been reported in the context of concomitant β-blocker therapy in the majority of cases, which may also support mechanism independent of β1 adrenergic receptor activation.[12] Clinical doses of β-blockers reduce, but do not eliminate, cardiac sympathetic stimulation. However, the adverse effects associated with the use of β blockers having partial agonist activity in patients with heart failure do not support a mechanism of CCM involving sympathetic activation and 'mild' β1 adrenergic receptor stimulation on the background of this therapy.

The effect of high-amplitude, biphasic CCM on intact beating hearts has been studied in a series of *in vivo* experiments.[25] The CCM current pulse (± 20 mA) was applied to the epicardial surface of the anterior and posterior left ventricular walls of canine hearts using a surgical approach. Global left ventricular function was recorded using pressure–volume analysis after 10 min of CCM treatment. Regional CCM stimulation using this experimental protocol induced a global increase in left ventricular contractility (as measured by the end-systolic pressure–volume relationship). Combined anterior and posterior CCM application enhanced the positive inotropic effect of the treatment compared with CCM application in either location alone. Global parameters of muscle relaxation were unaltered, although this observation might be expected because in a normal heart the threshold to achieve increased relaxation is high compared with that in a failing heart. Most importantly, no alteration in peripheral vascular resistance was detected during CCM application, excluding any 'off-target' vascular effect, given the theoretical potential for systemic neural reflex activation following cardiac neural stimulation.[25]

Clearly, more work is required to clarify the role of cardiac sympathetic nerve activation and the direct myocardial effects of CCM electrical pulses. However, the reader should note that the aforementioned mechanistic studies applied CCM pulses to the myocardium at much higher doses than does the currently licenced clinical system.

Animal studies using the clinical protocol

Acute regional effects

The current clinical CCM protocol, applied using the Optimizer® II device, has also been studied in a canine model of chronic heart failure secondary to diffuse ischaemic injury (induced by serial microembolizations). This model has provided considerable insight into the effects of CCM.[22] Acute application of biphasic CCM voltage pulses to the right side of the interventricular septum for 2 h reduced left ventricular dilatation (as measured by biplanar ventriculography) and increased LVEF from 26 ± 1% to 31 ± 2%.[22] These effects were associated with increased phosphorylation of phospholamban within the directly treated site (Figure 4b), suggesting that inhibition of SERCA2a by phosphorylated phospholamban had been relieved, thereby enhancing the activity of SERCA2a and increasing Ca^{2+} reuptake into the sarcoplasmic reticulum during diastole. This effect of phospholamban phosphorylation was limited to the local site of CCM delivery; the remote posterior wall myocardium did not show a change in phospholamban phosphorylation at this early (2 h) treatment time point (Figure 4b).[22] Again, acute β1 adrenergic receptor activation via cardiac sympathetic nerve stimulation might conceivably also lead to enhanced phospholamban phosphorylation, although other features do suggest that this pathway is not the sole mechanism (for example, the reverse remodelling of the gene expression abnormalities).[26,27]

Given the positive inotropic effect of a clinical CCM protocol in the intact failing heart, the investigators assessed the metabolic efficiency by recording the myocardial oxygen consumption (MVO_2).[28] Increased ventricular contractility was not associated with a harmful increase in MVO_2, such as that seen with dobutamine, implying that CCM could achieve a positive inotropic effect in a metabolically neutral (or even metabolically efficient) manner. Critically, these preclinical findings were replicated in a cohort of patients with heart failure during the same study.[28] These observations complement those that suggest enhanced SERCA2a activity is responsible for the action of CCM, and oppose the hypothesis that noredrenaline release mediated by the cardiac sympathetic nerve is the sole mechanism explaining the benefits of CCM. Consistent with other findings, increasing SERCA2a expression and activity in failing hearts using gene transfer can increase contractility, while not deleteriously affecting cardiac metabolic demand.[9,29]

However, a major limitation remains when extrapolating from the results of the early CCM studies, which used very different CCM protocols, to studies using the clinical protocol. Early studies of *ex vivo* papillary muscle preparations used high-amplitude, biphasic, current-pulse protocols, whereas application of low-amplitude, clinical CCM voltage pulses fails to induce an immediately detectable change in ventricular function in the large mammalian heart. However, all *in vivo* and *ex vivo* studies of CCM in intact hearts rapidly induce a positive inotropic effect that lasts up to several minutes after CCM is stopped, regardless of the pulse protocol used. One explanation is that Ca^{2+}-dependent changes do still occur in large hearts, but when the amplitude of stimulation is low, the magnitude of these changes is also reduced. Several minutes of treatment of a large heart with low-amplitude CCM voltage pulses are, therefore, required to alter contractility via a Ca^{2+}-dependent mechanism, particularly if alterations in the Ca^{2+} flux are required to affect global cardiac function, as discussed below.

Alternatively, other mechanisms might be required to explain the effects of the clinical CCM protocol in a large mammalian heart. Given the acute changes in phospholamban phosphorylation in response to CCM, the enzymatic activities of several critical kinases and/or phosphatases in the cardiomyocyte might also conceivably be voltage-sensitive. Cardiomyocyte contractility is

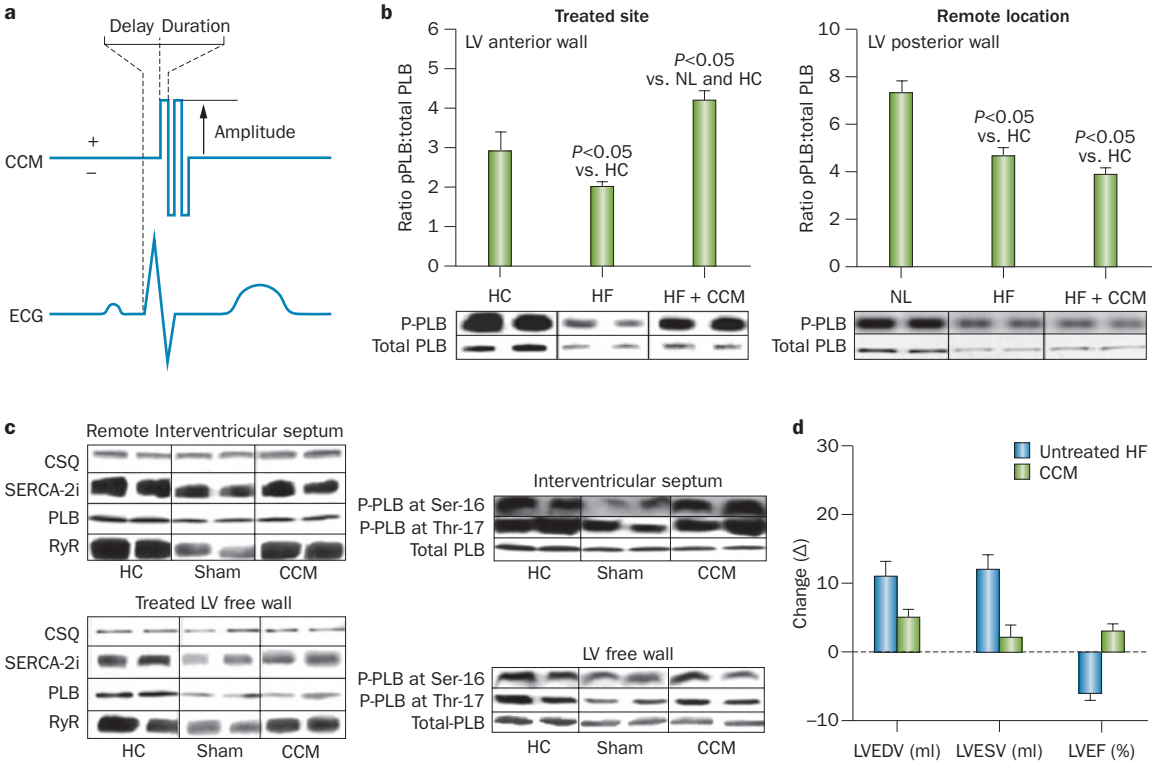

Figure 4 | Acute and chronic effects of clinical biphasic CCM voltage pulses *in vivo* in experimental models of heart failure. **a** | A clinical CCM double biphasic voltage pulse protocol. **b** | Acute increase in phosphorylation of the SERCA2 regulatory protein PLB in the treated region (interventricular septum, left panel) after 2 h of CCM therapy in a canine model of heart failure, with absent effect in remote myocardium (LV free wall, right panel). **c** | Effects of chronic CCM treatment *in vivo*. Application of the clinical CCM protocol induces biochemical reverse remodelling, indicated by increased expression of SERCA2A, PLB, and RyR proteins, which remained suppressed in untreated heart failure. Changes were noted in both directly treated (left panel, below) and remote regions (left panel, above). Increased phosphorylation of PLB was also evident in both directly treated (central panel, above) and remote regions (central panel, below) at 3 months of *in vivo* CCM treatment, in contrast to the localized effects of acute application, shown in b.[22] **d** | The effects of chronic CCM treatment with a single biphasic voltage pulse upon structural remodelling in a canine model of progressive heart failure. Progressive dilatation of the left ventricle and reduction in LVEF are both abrogated by chronic CCM therapy. Abbreviations: CCM, cardiac contractility modulation; CSQ, calsequestrin (loading control); ECG, electrocardiography; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HC, healthy controls; HF, heart failure; LV, left ventricular; PLB, cardiac phospholamban; pPLB, phosphorylated cardiac phospholamban; RyR, ryanodine receptor. Permission obtained for panels b and c from Elsevier Ltd © Imai, I. *et al. J. Am. Coll. Cardiol.* **49**, 2120–2128 (2007).[22] Permission obtained for panel d from Oxford University Press © Morita, H *et al.* Long-term effects of non-excitory cardiac contractility modulation electric signals on the progression of heart failure in dogs. *Eur. J. Heart Fail.* **6**, 145–150 (2004).[30]

regulated by the phosphorylation status of several key proteins (including phospholamban, ryanodine receptors, LTCCs, troponin I inhibitor-1 and β-adrenergic receptors) via a number of pathways.[15,20,21] Repetitive, biphasic voltage pulses during the absolute refractory period might modify the balance of kinase and phosphatase activity in the cardiomyocyte to favour a positive inotropic state, similar to that induced by increased phospholamban phosphorylation.

Focal CCM induces global reverse remodelling

Application of low-amplitude CCM voltage pulses immediately alters myocardial Ca^{2+} cycling, phospholamban phosphorylation, and contractility at the site of application. However, after 3 months of chronic CCM treatment, an augmented response in these parameters is evident across the whole canine heart (Figure 4c). Notably, these changes were accompanied by a demonstrable improvement in global markers of left ventricular size and function, including end-systolic volume, stroke volume, and LVEF, compared with the values in CCM-untreated dogs with heart failure, which demonstrated progression of ventricular dysfunction.[30] Furthermore, the expression of important heart failure biomarkers decreases in CCM-treated animals—interestingly, in both local (stimulated) areas and distant regions. For example, the expression of genes encoding atrial and B-type natriuretic peptides, levels of which are increased during heart failure, was restored to normal or near-normal levels after CCM. Additionally, the expression of other genes known to be perturbed in heart failure, such as *ADRB1, MYH6, ATP2A2, RyR2, PLN, S100A1*, and *SRI* (encoding the β1 adrenergic receptor, myosin-6, SERCA2a, ryanodine receptor 2, phospholamban, S100-A1, and sorcin,

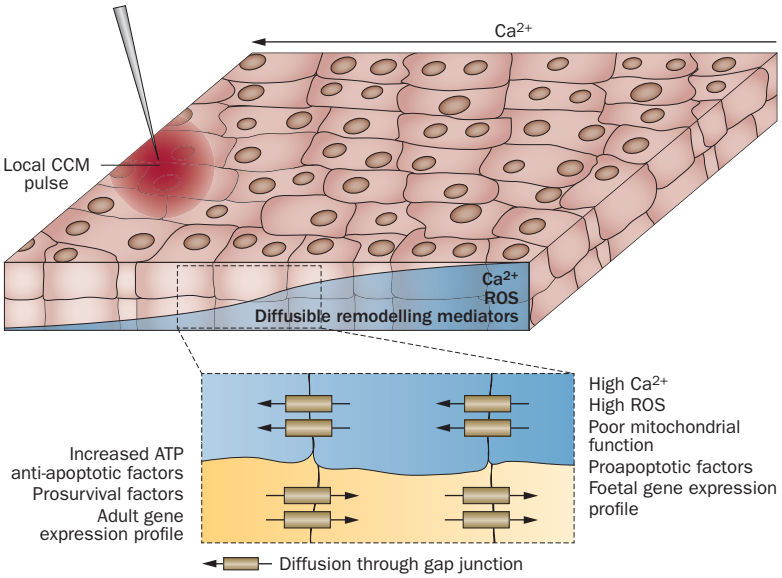

Figure 5 | The conjectured influence of CCM electrical pulses on intact ventricular myocardium. Local application of CCM is thought to induce a molecular and metabolic sink for the elevated diastolic Ca^{2+}, ROS and other abnormalities associated with the pathophysiology of the failing myocardium. Intercellular gradients lead to the diffusion of various mediators across gap junctions, acting in a source–sink relationship to ameliorate the harmful milieu of the failing myocardium adjacent to the region of CCM application (inset). Over time, chronic CCM therapy is thought to generate gradients that enable propagation of reverse remodelling throughout the myocardium. Abbreviations: CCM, cardiac contractility modulation; ROS, reactive oxygen species.

respectively), were all improved after CCM therapy (for examples see Figure 4c). Protein levels matched changes in gene expression, and phospholamban phosphorylation was also normalized after CCM treatment.[22,26] Expression and phosphorylation of NCX, which was increased in failing hearts and potentially contributed to arrhythmias in animals with untreated heart failure, normalized in CCM-treated hearts.[27] The changes in gene expression of cardiac-specific Ca^{2+} proteins and natriuretic peptides observed in a large animal model were confirmed in biopsy samples from CCM-treated patients with chronic heart failure.[31] Many parallel studies have shown that restoring expression of either SERCA2a or S100-A1, using virally mediated gene transfer, can initiate and improve reverse remodelling of the failing heart in an energetically beneficial manner.[5,32–36] Additional studies have compared CCM treatment with conventional β-blocker therapy in dogs with heart failure, and found that the interventions had comparable benefits when administered as monotherapies, and additive effects on molecular and functional reverse remodelling when used concurrently.[22]

Another possible mode of action underpinning the chronic effects of CCM treatment is its ability to reverse the overexpression of myocardial matrix metalloproteinases (MMPs), which are upregulated in the failing heart. CCM treatment reduced MMP upregulation, which was associated with a reduction in the density of myocardial fibrosis observed in histological analysis of failing hearts.[22,37] MMPs are implicated in the pathological remodelling of the extracellular matrix, deposition of fibrosis, and adverse ventricular remodelling. Amelioration of pathological MMP activation might reflect beneficial effect.

In summary, these findings suggest that chronic treatment with low-amplitude, double biphasic CCM voltage pulses delivered in the absolute refractory period initiates reverse remodelling that is beneficial to the failing heart. Simultaneously, CCM can provide the benefit of acute and sustained positive inotropic effects, analogous to those observed in CRT, but without the drawbacks of pharmacological positive inotropes, which fail to achieve reverse remodelling and increase metabolic oxygen consumption. In addition, once reverse remodelling has been initiated, the process is self-sustaining and potentially self-amplifying, perhaps via recovery of SERCA2a and RyR function. Other studies intervening specifically on these elements of cardiac SR Ca^{2+} physiology have imparted durable beneficial effects in a variety of heart failure models and lead to reverse remodelling. However, although the molecular changes reported in CCM-treated failing hearts are typical of a beneficial reverse remodelling profile, they do not provide any further insight into how an energy pulse elicits the favourable changes in genetic and protein expression that are eventually observed in the phenotypically reverse-remodelled heart.

The question of how local treatment of the interventricular septum can initiate a global remodelling effect also remains unanswered. Although the precise underlying mechanisms are unknown, parallels can be drawn with two other scenarios that might be relevant. Our research group recently reported that intramyocardial injection of an adenoviral vector containing the *ATP2A2* gene, which encodes SERCA2a, results in an altered molecular phenotype consistent with beneficial reverse remodelling in both the injected site and remote, noninjected regions.[33] We proposed that enhanced SERCA2 expression at the treatment site initiates localized reverse remodelling, which creates a cellular environment that acts as a metabolic 'sink' for the excess diastolic Ca^{2+} and ROS released by neighbouring failing tissue (Figure 5). The reverse-remodelled tissue might also become a source of diffusible mediators, which transfer from cell to cell via gap junctions located at the intercalated discs, and mediate propagation of the beneficial effects of CCM to neighbouring tissue (Figure 5). Given that CCM upregulates SERCA2a activity either directly or via increased phospholamban phosphorylation, and also increases S100-A1 and sorcin expression, conceivably similar mechanisms occur during focal CCM application and focally injected SERCA2a gene therapy. This insight could also explain why the acute effects of CCM are only observed in the locally stimulated region, whereas the molecular changes associated with reverse remodelling only reach remote areas of heart tissue during chronic treatment.

Clinical trial data

In the past 15 years, many clinical studies of CCM have been conducted in patients with heart failure who were

also receiving contemporary therapies. These studies were modelled after the analogous investigations of CRT in patients with QRS prolongation.

Early safety and efficacy studies

The acute haemodynamic response

Early clinical studies used short-term application of CCM signals via temporary transvenous pacing electrodes. The initial feasibility study of CCM included patients with heart failure and either ischaemic or nonischaemic cardiomyopathy with LVEF ≤35% who were undergoing a conventional electrophysiological procedure (either device implantation or investigation of ventricular or supraventricular tachycardia).[38] A dual-sensor micromanometer was used to simultaneously assess left ventricular and aortic pressures, and quadripolar leads were inserted into the right atrium and right ventricle for temporary dual-chamber pacing. A CCM device applied biphasic, nonexcitatory square wave signals triggered by local activation. The CCM current was 20–40 ms in duration, and applied 30–60 ms after detection of local activation. Stimulation occurred at 14 mA or the highest tolerated current without chest wall stimulation or patient-reported discomfort. Signals were either delivered to the left ventricle through an octapolar catheter implanted into the coronary sinus, the right ventricle via a bipolar lead or, in patients with left bundle branch block, to the left ventricle lead following biventricular pacing. After 2 h of CCM signal application, myocardial contractility (as measured by the maximal rate of rise in left ventricular pressure, dP/dt_{max}) was increased by 10%. This statistically significant increase in dP/dt_{max} was not affected by QRS duration and, in fact, in patients with left bundle branch block, this effect of CCM was additive to the improvement in contractility achieved with biventricular pacing alone.[38] This improvement in myocardial contractility was achieved with a neutral effect on coronary flow velocity and myocardial oxygen consumption (calculated using quantitative angiography), mirroring the results of studies of the acute haemodynamic effects of CRT.[28,39] Colour kinesis and acoustic boundary detection studies also demonstrated improvements in both regional and global cardiac function.[38] However, a limitation of the study was the use of dual-chamber right ventricle pacing as the control condition. Although this method of pacing facilitated standardization of the basal heart rate and ensured proper timing of the CCM signal application, it did introduce the well-characterized deleterious effects of right ventricular pacing (namely, a reduction in peak left ventricular pressure and dP/dt) into the participants' baseline haemodynamics.[40]

Long-term effects

The positive response to CCM therapy demonstrated by acute haemodynamic testing led to the initiation of long-term studies utilizing one of three iterations of the Optimizer® implantable CCM device. The Optimzer® devices consist of a pulse generator without pacing or defibrillation capabilities, a right atrial lead, and two active fixation leads placed in the apical and mid right ventricular septum (ideally in the anterior and posterior interventricular grooves, respectively). In addition to fluoroscopic guidance, researchers have used haemodynamic guidance to position leads at locations resulting in maximal values of dP/dt_{max}. Generally, investigators have required the demonstration of a ≥5% increase in dP/dt_{max} on test stimulation to proceed with CCM device implantation. Although no data suggest that such an acute haemodynamic response correlates with long-term improvements in functional capacity or ventricular remodelling, it does provide some reassurance that the selected lead location can favourably influence left ventricular haemodynamics. The proportion of patients who do not undergo device implantation because a ≥5% increase in dP/dt_{max} cannot be demonstrated (termed haemodynamic failure) has varied between 5% and 10%.[41]

All Optimzer® devices use safety algorithms, incorporating regional stored electrograms from the atrial and ventricular leads, to precisely apply CCM signals during the absolute refractory period of sinus beats and to abolish CCM signals during ectopic beats or arrhythmias, thereby avoiding signal application during the relative refractory period (when electrical stimulation might provoke ventricular arrhythmias). Studies to date have also excluded patients with atrial fibrillation or ≥8,900 premature ventricular contractions per 24 h on preoperative Holter monitoring. Generally, trials have also excluded patients with recent myocardial infarction and those who are candidates for CRT, typically defined as patients with a QRS duration >140 ms. Preliminary data have suggested a dose–response effect of increasing durations of CCM; therefore, consecutive studies have incrementally increased the duration of therapy. The high energy of CCM signals—roughly 50–100 times that applied in conventional pacing applications—required early versions of the device to be replaced every 6–8 months, a drawback that has since been overcome by the use of transcutaneously rechargeable batteries.

The first long-term clinical experience with CCM signal application was described in two unblinded, noncontrolled feasibility studies (FIX-HF3) of the Optimizer® II system in patients with ischaemic or nonischaemic cardiomyopathy. Participants in both studies had NYHA functional class III heart failure, QRS duration <140 ms, LVEF ≤35%, left ventricular end-diastolic dimensions ≥55 mm, and a baseline VO_{2max} ≥11 ml·kg^{-1}/min, despite ≥3 months of optimal medical therapy.[42,43] In the first of these studies, 25 patients underwent 3 h of CCM signal application daily.[43] The patients required an average of 1.9 ± 1.7 attempts at right ventricular lead positioning to achieve an adequate acute haemodynamic response (≥5% increase in dP/dt_{max}).[43] After 8 weeks of follow-up, 19 of the 25 patients demonstrated a dramatic improvement in NYHA functional class, LVEF (from 22 ± 7% to 28 ± 8%; $P = 0.0002$), and overall quality of life assessed using the Minnesota Living With Heart Failure (MLWTF) questionnaire (scores decreased from 43 ± 22 to 25 ± 18; $P = 0.001$).

Assessments of LVEF were made at least 12 h after interruption of the CCM signal application, thereby confirming at least short-term persistence of remodelling effects while off active therapy. However, as the researchers themselves noted, these data are inadequate to clearly establish the optimal daily duration and intensity of CCM therapy, and they called for dose-ranging studies to be conducted.

The second trial was a substudy of FIX-HF-3.[42] After the initial 8-week period of CCM therapy, a subgroup of 13 patients went on to complete a 24-week extension phase, during which they underwent seven equally spaced 1 h periods of CCM therapy daily. This study achieved its primary end point by showing that CCM signal application reliably occurred in >70% of sinus beats. These patients' LVEF improved from 22.7 ± 7% to 28 ± 7% in the first phase, and to 37 ± 13% in the second phase ($P = 0.004$). Peak VO_2 also significantly improved from 13.7 ± 1.1 ml·kg^{-1}/min to 14.9 ± 1.9 ml·kg^{-1}/min in the first phase, and again to 16.2 ± 2.4 ml·kg^{-1}/min in the second phase ($P = 0.037$) at study completion. Exercise tolerance, as measured by 6 min walk distances, increased by 14%. Mean NYHA functional class also improved, from 3.0 to 1.5 ± 0.7 ($P < 0.001$). Interestingly, although all clinical end points showed further improvements in mean values between the first and second phases, these changes were accompanied by increased variability (dispersion from the mean), highlighting the need for individualized therapy and further investigation to determine which patients warrant intensification of CCM therapy.

The primary safety end point of the FIX-HF-3 study was assessment of proarrhythmic potential, which was conducted with Holter monitoring. Ventricular and supraventricular tachyarrhythmias did not show a significant increase; in fact, a trend towards a reduction in these arrhythmias was noted in the second phase of the study. In one patient, atrial undersensing led to in device inhibition, which led to clinical deterioration 3 weeks following implantation. However, this decline was promptly alleviated by the restoration of CCM therapy. One pocket infection, one episode of pocket stimulation requiring a reduction in the device output, and one episode of phrenic nerve stimulation necessitating lead repositioning were recorded. Two fatalities during the study were attributed to sudden cardiac death in patients with ischaemic cardiomyopathy, and were not temporally related to CCM signal application. Notably, FIX-HF-3 was performed while national guidelines for implantable cardioverter-defibrillator (ICD) therapy were still evolving; subsequent trials of CCM therapy have required study participants to already have ICDs. Finally, owing to its high energy consumption, the CCM device needed to be replaced in all patients within 1 year (mean 7 ± 3 months).

In addition to the consistent improvements in quality of life and functional capacity, a growing body of data show that left ventricular remodelling is associated with CCM therapy. Real-time 3D echocardiography and tissue Doppler imaging have been employed to assess changes in regional and global left ventricular function accompanying the long-term application of CCM signals.[44] At 3 months of follow-up, significant improvements were observed in left ventricular end-systolic volume (–11.5 ± 10.5%; $P < 0.001$), left ventricular end-diastolic volume (–5.5 ± 8.0%; $P = 0.002$), and LVEF (4.8 ± 3.6%; $P < 0.001$). Improvement of left ventricular systolic function was also demonstrated by tissue Doppler imaging, which showed significantly increased mean values for systolic velocity in all 12 ventricular segments ($P < 0.001$). Recapitulating the findings from animal studies, CCM seemed to exert its effects without demonstrable effects on regional or global diastolic function, and without causing significant changes in peak early diastolic velocity. Similarly, no changes were demonstrated in systolic or diastolic mechanical synchrony, as evidenced by time to peak systolic and early diastolic velocities, respectively.[44]

Changes in left ventricular remodelling introduced by CCM and CRT in patients with varying QRS durations have also been explored. Improvements in the left ventricular end-systolic volume were similar in patients with QRS durations <120 ms receiving CCM and those with QRS durations of 120–150 ms receiving CRT. However, the greatest improvements in left ventricular remodelling occurred in the patients with a QRS duration >150 ms who received CRT.[45]

Randomized clinical trials

Randomized trials investigating the use of CCM therapy were modelled on the pivotal studies of CRT. In addition, based on early evidence of a dose–response effect, these trials have employed progressively longer durations of CCM signal application.

FIX-HF-5 feasibility substudy

FIX-HF-5 was a multicentre, randomized, double-blind, feasibility study to assess the safety and efficacy of CCM over a follow-up period of 6 months.[46] 52 patients with NYHA functional class III–IV heart failure, LVEF ≤35% on optimal medical therapy, and using ICD therapy were enrolled. Patients undergoing, or deemed candidates for, CRT therapy were excluded, as were those with a baseline peak VO_2 <11 ml·kg^{-1}/min, recent myocardial infarction, high-frequency premature ventricular contractions, or atrial fibrillation. After a stabilization period, patients were randomly assigned to either CCM treatment, with five 1 h periods of stimulation interspersed throughout the day, or sham treatment in which the device was implanted but remained inactive. Blinded clinical assessments were performed at 3 months and 6 months to assess LVEF, peak VO_2, and the ventilator anaerobic threshold (VAT). A CCM device was implanted in a total of 52 patients, 49 of whom took part in the randomized trial. Baseline characteristics differed between the two groups: LVEF, peak VO_2, and VAT were significantly lower and left ventricular end diastolic dimension was significantly higher in the active treatment group, which suggests that these patients had more baseline impairment in their cardiac function.

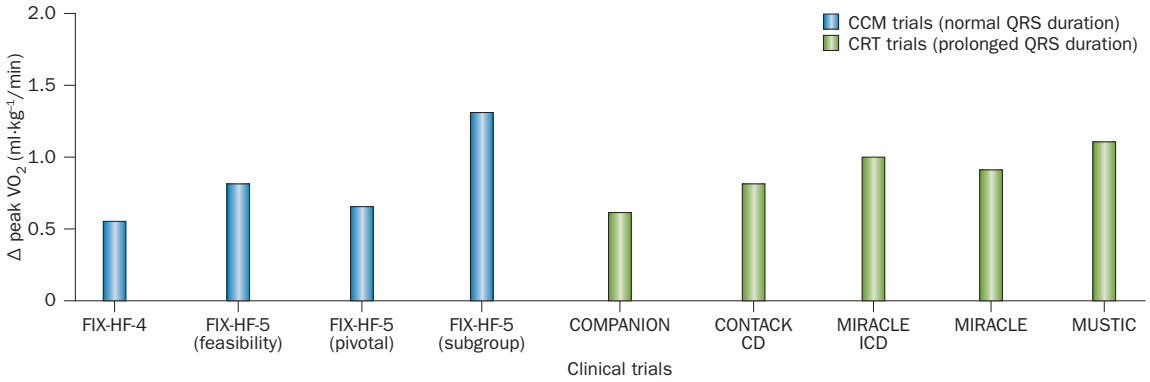

Figure 6 | Comparison of the effects of CCM and CRT on peak VO_2 in clinical trials. Patient populations and study designs were similar, except that the CRT trials included patients with prolonged QRS duration, whereas the CCM trials included only patients with normal QRS durations. Abbreviations: Δ peak VO_2, change in oxygen consumption; CCM, cardiac contractility modulation; COMPANION, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CON-TAK CD, Contak cardioverter-defibrillator trial; CRT, cardiac resynchronization therapy; FIX-HF, Evaluation of the Safety and Effectiveness of the Optimizer® System in Subjects With Heart Failure; MIRACLE, Multicentre InSync Randomized Clinical Evaluation; MIRACLE ICD, Multicentre InSync Implantable Cardioverter-Defibrillator Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathy.[54] Used with kind permission from Springer Science and Business Media © Burkhoff, D. Does contractility modulation have a role in the treatment of heart failure? *Curr. Heart Fail. Rep.* **8**, 260–265 (2011).

The device was generally well tolerated and adverse effects were minimal. Nonserious adverse events included lead dislodgements, pericardial effusion, one inappropriate ICD firing, and two cases of pocket infection. Holter monitoring showed no significant changes in heart rate, ectopy, or arrhythmia. A trend towards a reduction in hospitalization-free survival was observed at 6 months (62% in the control group versus 84% in the active treatment group). Clinically relevant improvements in both NYHA functional class and MLWHF quality of life scores were seen in both study groups, suggesting the presence of a substantial placebo effect. No statistically significant differences were observed between the groups in 6 min walk distances, peak VO_2, VAT or LVEF; however, there were trends towards improvement in these variables in the treatment group. The design of this study was based on that of the MIRACLE study of CRT, which demonstrated similar directions and magnitudes of effects on 6 min walk distances and hospitalization-free survival.[47] To what extent the failure of FIX-HF-5 to demonstrate statistically significant changes in these variables was a result of the small sample sizes and baseline inequalities between the groups is unknown.[44]

FIX-HF-4

Two large-scale, prospective, randomized clinical trials have investigated the effects of CCM on exercise tolerance and quality of life in patients with advanced systolic heart failure. The first of these studies, FIX-HF-4, employed a double-blind crossover design modelled on the MUSTIC trial of CRT.[48,49] The design effectively overcame the prominent placebo effect observed in the FIX-HF-5 feasibility study.[46] After randomization, all 164 patients in the trial were implanted with the device and received 12 weeks of either active CCM or sham therapy, before receiving 12 weeks of the alternative therapy. After this 24-week blinded period, all patients were offered open-label CCM therapy. The CCM signal was applied for 7 h daily during active treatment.

Four patients died during the 24-week blinded portion of the study, and another nine patients withdrew owing to pocket infection or heart transplantation. One patient was excluded after randomization because they became eligible for CRT. The joint primary efficacy end points of the study were the change in peak VO_2 and quality of life scores (assessed using the MLWHF questionnaire). Interestingly, at 12 weeks, identical improvements in peak VO_2 were seen in both the control and treatment groups (0.4 $ml \cdot kg^{-1}/min$). Overall, all primary clinical end points showed matched improvements in the treatment and control groups at 12 weeks, again demonstrating the dramatic placebo effect described in FIX-HF-5. However, during the second 12-week blinded phase, VO_2 continued to increase in patients who had crossed over to the active treatment arm, while it decreased in patients who had crossed over to the control arm. Overall, mean peak VO_2 improved significantly while on active therapy by 0.52 ± 1.39 $ml \cdot kg^{-1}/min$ ($P = 0.032$) versus sham therapy. However, this change in peak VO_2 was modest relative to that observed at 3 months in major CRT trials, including MUSTIC (Figure 6). MLWHF scores improved in both active CCM and sham CCM groups, but more improvement was noted in those undergoing active treatment. Secondary measures of treatment efficacy, including 6 min walk distance and NYHA functional class, also improved. A potential limitation of FIX-HF-4 was the short duration of the study—only 3 months—which might have been insufficient to demonstrate maximal efficacy. In addition, the study size was too small to reliably rule out the presence of a carryover effect from the first to the second of the 12-week periods but, if present, such an effect would have only diluted the apparent treatment outcome.

FIX-HF-5 Pivotal trial

The largest CCM study to date is the multicentre FIX-HF-5 trial, which was conducted in the USA to assess the long-term safety and efficacy of the clinical CCM system. The Optimizer® III device used in FIX-HF-5 incorporated a transcutaneous rechargeable battery, which overcame one of the major limitations of prior iterations.[50] FIX-HF-5 included 428 patients with an LVEF ≤35% and NYHA functional class III or IV heart failure, despite receiving optimal medical therapy. All patients were in sinus rhythm and, like those in FIX-HF-4, were not candidates for CRT.

Peak VO_2 is often considered the gold standard prognostic marker in patients with heart failure. However, this parameter is both effort-dependent and highly influenced by the peripheral metabolism. The use of peak VO_2 as a surrogate end point in clinical trials has, therefore, largely been confined to double-blinded studies in the CRT literature.[47,49,51] In contrast to prior CCM clinical trials, which did incorporate a double-blind crossover design, the need for weekly recharging of the Optimizer®III device in FIX-HF-5 was considered a barrier to effective blinding and the long-term implantation of a nonfunctional device was deemed impractical and unethical. Thus, in the absence of blinding, the FIX-HF-5 investigators (at the behest of the FDA) selected the change in VAT, measured on cardiopulmonary exercise testing, as an objective, effort-independent primary efficacy end point. VAT assessments were made by two independent observers who were blinded to the patients' study group assignments. Patients with a ≥20% improvement in VAT at 24 weeks of follow-up were classified as responders. VAT had decreased by 0.14 ml·kg^{-1}/min in both groups at 24 weeks, with no significant difference in the rates of responders (17.6% in the CCM group versus 11.7% in the optimal medical therapy group; $P = 0.093$). However, despite its advantages, VAT has clear limitations resulting from interobserver and intraobserver variability in its measurement.[49] Although mean differences between readers were small, and repeat readings initially seemed to be highly correlated in both interobserver and intraobserver comparisons, agreement was poor when these comparisons were further assessed by Bland–Altman analysis.[52] Limits of agreement in VAT measurements of up to 200 ml (representing limits of agreement ranging from 17% to 27%) and coefficients of variation in the 5–10% range were observed. These errors were reduced in the final VAT determination with the addition of a third reader.[52]

In contrast to VAT, ventilatory efficiency (VE/VCO_2) has consistently demonstrated equivalency to peak VO_2 in predicting morbidity and mortality associated with heart failure, and—unlike peak VO_2—is an effort-independent variable.[53] However, no precedent exists for the use of VE/VCO_2 as a surrogate efficacy end point in these types of trials. Similarly, despite the perceived advantages of VAT, no precedent exists for its use as a surrogate efficacy end point in the heart failure literature.[54] The use of responder analysis in CCM trials is also controversial, owing to the lack of a precedent for this approach in the CRT literature, and the questionable utility of arbitrarily defined thresholds that are not linked to hard clinical outcomes. The primary safety end point of FIX-HF-5, assessed by noninferiority analysis, was a composite of all-cause mortality and all-cause hospitalization at 50 weeks. Using intent-to-treat analysis, a 48.4% event rate was demonstrated in the optimal medical therapy group versus a 52.1% event rate in the CCM group, which satisfied the noninferiority criterion ($P = 0.03$). Moreover, although the study failed to meet its primary VAT-based efficacy end point, CCM therapy was associated with significant improvements in both peak VO_2 (0.65 ml·kg^{-1}/min, $P = 0.024$) and MLWHF questionnaire scores (a decrease of 9.7 points, $P < 0.0001$) versus optimal medical therapy. In summary, FIX-HF-5 showed that CCM therapy was safe but did not conclusively demonstrate its statistical efficacy at 1 year of follow-up.[50]

A meta-analysis of data from the three randomized clinical trials discussed above, which included data from a total of 641 patients, was published in 2012.[55] Pooled analysis again failed to demonstrate a significant improvement in either all-cause mortality (RR 1.19, 95% CI 0.50–2.86) or all-cause hospitalization (RR 0.64, 95% CI 0.38–1.08).[55]

Long-term survival data

Notably, adoption of CRT began after publication of the MIRACLE trial, which demonstrated only that CRT resulted in improvements in quality of life and functional capacity.[47] It was the CARE-HF trial results (published 3 years after MIRACLE) that first conclusively demonstrated the reductions in hospitalizations and all-cause mortality that have cemented the role of CRT in the heart failure armamentarium.[56] Importantly, the CARE-HF Kaplan–Meier survival curves do not demonstrate the emergence of a mortality benefit until approximately 1 year after the initiation of CRT.[56]

Long-term outcome data from 54 patients with CCM devices implanted between 2003 and 2010 at a single centre has also been published.[57] Following a mean duration of CCM therapy of 20 months (95% CI 17–25 months) Kaplan–Meier analysis showed that the median survival was 992 days (33.1 months) and the mean death rate was 18.4% per year in this cohort. Despite the lack of a control group, all-cause mortality was precisely predicted by the Seattle Heart Failure Model (SHFM).[57] However, the study was limited by its small sample size, heterogeneous group of participants (which included patients with narrow QRS complexes and CRT nonresponders), and a predominance of patients with NYHA functional class III–IV heart failure (by contrast, the original SHFM derivation cohort largely comprised patients with NYHA functional class II–III heart failure).[58] Although these findings do not support a mortality benefit of CCM over standard medical therapy, they provide some evidence of long-term safety of a device already known to improve quality of life. Clearly, large, long-term, prospective studies are necessary to firmly establish the effect of CCM therapy on hospitalizations for, and mortality from, heart failure.

Future applications of CCM

Prospective CCM clinical trials have demonstrated a consistent improvement in peak exercise tolerance, and crossover double-blinded trials show improvements in NYHA functional class and MLWHF questionnaire scores. Investigators have rightly suggested that the magnitude of the improvement in peak VO_2 is similar to that achieved with CRT in patients with prolonged QRS durations who are otherwise medically similar (Figure 6). However, we now know that in a selected subgroup of CRT 'super-responders'—principally patients with left bundle branch block and a QRS duration >150 ms—substantially larger improvements in peak VO_2 can be achieved. In one study, a 2.46 ml·kg^{-1}/min improvement in peak VO_2 was achieved with left ventricular pacing in patients with NYHA functional class II heart failure and a QRS duration >150 ms.[59] The pool of potential candidates for CCM—currently, all patients with systolic heart failure and a QRS duration <150 ms is perhaps too broad, and the lack of a more-narrowly defined target population might actually hinder progress in the field. Regulatory bodies might be unwilling to approve a device therapy for such a large population; therefore, efforts to identify the optimal CCM candidate could help to accelerate acceptance of this technology.

Prespecified subgroup analysis from FIX-HF-5 demonstrated that patients with moderate heart failure (LVEF ≥25% and NYHA functional class III) had significant improvements in both VAT and peak VO_2.[60] In this subset, the improvement in peak VO_2 was deemed unlikely to reflect changes in effort, as this parameter did not correlate with the (nonsignificant) changes in the respiratory exchange ratio. This hypothesis-generating *post-hoc* analysis inspired the development of a new randomized, parallel, open-label trial, FIX-HF-5B, which is currently underway.[61] Why CCM seems to be more effective in patients with moderate rather than severe heart failure is unclear. Investigators have speculated that the benefits of CCM are, like those of other therapies for heart failure, concentrated in patients with moderate heart failure and relatively high LVEFs, because the regional effects provided by multisite right ventricle CCM signals are less likely to induce global benefits in patients with severe heart failure who, by inference, have more-dilated ventricles.[60]

In patients with advanced heart failure, expression of gap junction proteins and their activity are both reduced, which slows signal conduction and contributes to arrhythmia generation.[62] This gap junction uncoupling might also limit the propagation of reverse remodelling from the CCM-treated local site to remote ventricular tissue. Preclinical studies suggest the maximal effect of CCM therapy might be garnered before the fall in SERCA2a functionality and gap junction expression, and chamber dilatation impairs the capability of regional changes to exert global effects.[62] Whether these limitations could be overcome by using multiple sites or left ventricular epicardial sites of CCM signal application is not known, but these sites are associated with obvious technical barriers to the application of high currents. An alternative way of looking at this subset of patients can be borrowed from the lessons we have learned from CRT. As clinicians, we strive to treat or reverse a disease process, but we now know that some early interventions can alter the trajectory of a disease and/or slow the speed of its progression.

The above observations also suggest that CCM might be beneficial (in extreme situations) in patients in the very early stages of heart failure, perhaps even in those with asymptomatic left ventricular dysfunction. This theory is bolstered by the fact that the acute haemodynamic benefits of CCM are apparent even in normal hearts, and the mechanical and gene-expression derangements that are antecedent to overt heart failure are also present in patients with asymptomatic left ventricular dysfunction. Although it is associated with less than half the mortality of overt heart failure, asymptomatic left ventricular dysfunction remains a highly morbid condition, as evinced by the Framingham data and results of the SOLVD prevention trial. Untreated asymptomatic left ventricular dysfunction progressed to overt heart failure at an annual rate of 10%, with an annual risk of death or hospitalization for heart failure of 8%.[63] Alternatively, given that the acute haemodynamic benefits of CCM therapy occur almost instantaneously, and are achieved with a neutral effect on myocardial energetics, temporary CCM signal application could provide an alternative to conventional inotropic drug therapy in patients who present with acute decompensated heart failure and mild cardiogenic shock.

Additionally, CCM has been successfully used to treat a patient with heart failure who did not respond to CRT.[64] The efficacy of CCM in this subgroup of patients will require additional investigation, as individuals who are eligible for CRT have been excluded from CCM trials to date. CCM has also been used as an adjunctive therapy in patients who failed to respond to CRT.[65] In this study, 16 patients who had not responded to CRT (defined as persistent NYHA functional class III or IV symptoms, despite adequate biventricular pacing with sinus rhythm) underwent contralateral implantation of a CCM device.[65] After 3 months of CCM therapy, these patients had statistically significant reductions in mean NYHA class (from 3.4 ± 0.5 at baseline to 2.7 ± 0.4; P <0.01), left ventricular end-diastolic dimension (from 7.5 ± 0.8 cm at baseline to 7.26 ± 0.9 cm; P <0.03), and a statistically significant increase in LVEF (from 28.1 ± 7% at baseline to 31.3 ± 11%; P <0.03). Thus far, studies of CCM therapy have shown acceptable interactions with existing implantable cardiovascular devices. The ongoing FIX-HF-12 study will further examine the effects of CCM in this population of patients.

Finally, two unresolved pragmatic considerations remain regarding the long-term benefits of CCM therapy. First, the current practice of repositioning leads until an increase in dP/dt_{max} of ≥5% is achieved is not evidence-based. No data suggest that this level of acute haemodynamic response has an effect on the long-term benefits of CCM therapy. A parallel can be drawn here with CRT, in which the patient's baseline dP/dt_{max}, value,

but not the acute benefit of CRT, is predictive of long term outcomes.[66] The second issue is that no proper dose-ranging studies have yet been conducted to guide optimal device therapy.

Conclusions

As optimal medical therapy evolves, identifying novel therapies that are associated with an incremental benefit on hard end points, such as mortality, has become increasingly challenging. The success of CRT has relied on its positive effects on long-term morbidity and mortality from heart failure. However, as demonstrated in the CRT literature, patients who derive symptomatic and acute haemodynamic benefit from device therapy might or might not derive a prognostic benefit.[66,67]

The Optimizer® system has been approved and is commercially available throughout much of Europe. Clinical trials of this device are ongoing in the USA, focusing on the effects of long-term CCM on morbidity and mortality from heart failure, and clarification of the effects of this therapy on exercise capacity and symptoms in patients with mild heart failure. Currently, with over 900 patients studied, the safety and efficacy of this approach seems to be acceptable. However, the ideal goals for any new therapy for heart failure are to favourably alter mortality as well as quality of life. More data on the long-term effects of CCM are clearly needed but, as was the case with CRT, the demonstration of a benefit of long-term CCM therapy in terms of a reduction in morbidity and mortality from heart failure might prove challenging in the absence of widespread application of this technology.

Whether CCM therapy is ready for integration into the routine management of heart failure can be distilled into a single question: can clinicians diverge from their long-standing preoccupation with reducing mortality from heart failure above all other end points, and embrace therapies that primarily improve how patients feel? If CCM ultimately fails to demonstrate concrete improvements in survival or hospitalizations for heart failure, it might still be a worthwhile therapy. However, the benefits, risks, and, unavoidably, the cost of CCM must be carefully weighed against those of other therapies that improve quality of life.[68,69]

Review criteria

We searched MEDLINE and PubMed for full-text original research articles and reviews in English focusing on cardiac contractility modulation and nonexcitatory myocardial stimulation published during 1969–2013. Search terms used included “cardiac contractility modulation”, “CCM”, “inotropic effects” and “absolute refractory period”, alone or in combination. The reference lists of all articles retrieved were examined to identify additional relevant citations. Experts in the field were queried for additional recommended references.

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Author contributions

The authors contributed equally to researching data for the article, and made substantial contributions to discussion of the content, writing, review, and editing of the manuscript before submission.