Cardiac contractility modulation for treatment of heart failure

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Summary

Cardiac contractility modulation has been studied for over a decade to treat heart failure. This article provided an overview of the suggested mechanisms of action and current evidence of efficacy, and discusses the clinical perspectives of this therapy.

Key words: cardiac contractility modulation; heart failure; cardiac pacing.

Introduction

Cardiac contractility modulation (CCM) is an electrical device-based approach proposed to enhance ventricular contractile strength of the failing myocardium, independently of synchrony of myocardial contraction. [1–3] CCM signals are non-excitatory, relatively high-voltage electrical impulses applied during the myocardial absolute refractory period. These signals do not initiate a new contraction or affect activation sequence, but modify the entry of calcium into the cardiomyocyte and enhance its contractility. CCM has been tested in several experimental and clinical studies that have explored the underlying molecular mechanism associated with the therapy and evaluated its safety and effectiveness [4–7]. Two recent multi-centre randomised controlled clinical trials may reposition this therapy in the therapeutic arsenal of heart failure[8, 9].
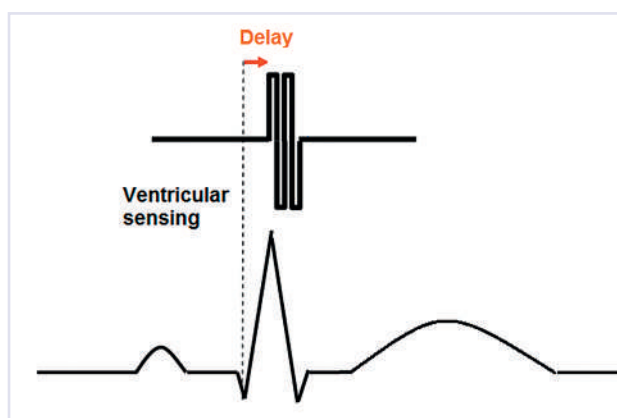
Suggested mechanisms

CCM signals are relatively high-voltage electrical impulses delivered to the myocardium 30–40 ms after detection of local myocardial activation during the absolute refractory period (fig. 1). A bi-phasic square wave pulse is the most common waveform utilised. The CCM pulses can be described by parameters of phase duration, delay from activation and signal amplitude. Studies of the mechanisms underlying the acute and prolonged effects of CCM signals have focused on their impact on action potentials, peak intracellular calcium, calcium loading of the sarcoplasmic reticulum and gene expression. CCM pulses do not induce additional action potentials nor cause contraction of the myocyte, but are believed to improve myofilament efficacy and enhance contractility by increasing the entry of calcium into the cardiomyocyte [1, 5, 10]. CCM has been associated with long-term improvement in left ventricular systolic function and remodelling, which has been attributed to normalising phosphorylation of key proteins and improving expression of proteins involved in the regulation of calcium cycling and contraction [7, 11]. These favourable effects are observed within a short period of time in the region where CCM signals are delivered and are more delayed in remote areas [2, 12].

Figure 1

Cardiac contractility modulating (CCM) signals with biphasic pulses delivered after a defined delay from detection of local ventricular electrical activation.

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Experimental data

Experimental studies have been conducted to analyse the acute and long-term impact of CCM in isolated papillary muscle, in animals with normal hearts and mostly in dogs with chronic heart failure produced by intracoronary microembolisations[1, 5, 12].

Acute studies have been undertaken to evaluate the haemodynamic impact of regional CCM signal delivery on regional contractile function and on global contractility as well as to assess the mechanisms involved in the described improvement. These studies demonstrated that CCM delivery acutely increases phosphorylation of phospholamban at the pacing site (but not at remote sites) [12] and significantly increases LV contractility [2, 5, 13].

After months of CCM delivery for several hours daily, there are data that indicate an increase in gene expression of phosphorylated phospholamban, both at and remote from the pacing site [12] as well as favourable histopathological effects [12] (e.g., fibrosis) and reverse remodelling with improved LV volumes and ejection fraction [12, 14].

Observational studies in humans

The initial clinical study in 2002 of CCM signals in humans involved short-term CCM signal application using temporarily placed electrodes in heart failure patients having either ischaemic or idiopathic cardiomyopathy [15]. An acute positive haemodynamic effect resulting from delivery of CCM was demonstrated, with an approximate 10% increase in maximum dP/dT and aortic pulse pressure. This effect was independent of baseline QRS duration, whether CCM was delivered via a coronary vein or in the right ventricle, and appeared to be additive to biventricular stimulation when both were combined. Two years later, the same authors demonstrated the feasibility of long-term application of CCM in humans with severe heart failure [16]. Within the limit of an average of nine months follow-up, no major adverse events were observed.

Mechanistic data of subsequent studies demonstrated reversal of maladaptive fetal gene programmes with CCM (A- and B-type natriuretic peptides, p38 mitogen activated protein kinase MHC, SERCA-2a, phospholamban, and ryanodine receptors) [7]. CCM has been shown to acutely increase left ventricular contractility without increasing myocardial oxygen consumption [17]. After several months of CCM, left ventricular ejection fraction improved by about 5% in absolute terms [16, 18, 19] and induced reverse remodelling of left ventricular volumes [18]. Improvement in clinical parameters such as quality of life, NYHA class, and exercise capacity has been reported [16, 18, 19]. In a small series of 16 non-responders to cardiac resynchronisation therapy, CCM has shown an acute increase in left ventricular contractility as well as a significant improvement in ejection fraction and NYHA class [20].

Randomised studies

The first randomised, double-blind crossover study including 49 heart failure patients demonstrated neutral results in terms of NYHA class, exercise capacity and quality of life comparing 6-month CCM to no CCM [21]. However, this was a feasibility study with a limited number of patients, and did not allow drawing firm conclusions regarding effectiveness of the therapy to improve clinical outcome.

FIX-CHF-4

This double-blind study included 164 heart failure patients in Europe with an ejection fraction ≤35%, NYHA Class II to III who were ineligible for cardiac resynchronisation therapy [9]. All patients were implanted with the OPTIMIZER™ system. The trial had a crossover design with two 3-month periods with and without treatment. Analysis at the end of the active and sham treatment periods showed significantly improved peak oxygen consumption and six minute walk tests and Minnesota Living with HF Questionnaire with CCM, although endpoints improved similarly during the first three months whether CCM was turned on or off, and there were no significant differences in NYHA. The study population was limited in size and therefore these results may be statistically underpowered.
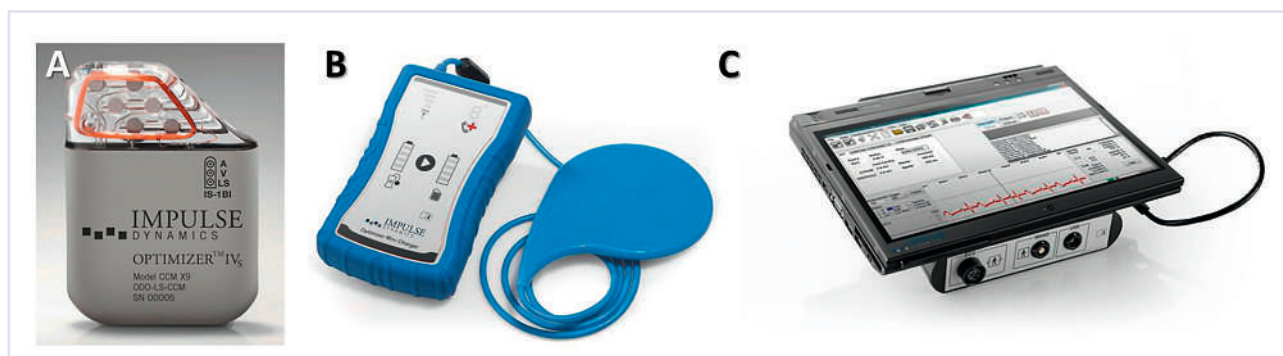
FIX-HF-5

This prospective, randomised, parallel-group, controlled trial conducted at 50 centres in the United States tested the 1-year safety and efficacy of CCM treatment.[8] A total of 428 patients with NYHA Class III to IV, ejection fraction ≤35%, and a narrow QRS were randomised to CCM (n = 215) or to no CCM (n = 213). The safety end point, a composite of all-cause mortality and all-cause hospitalisations in a non-inferiority analysis, was satisfied (but this also indicated no improvement in these endpoints). In the overall population, CCM significantly improved peak VO2, Minnesota Living With Heart Failure Questionnaire and NYHA class but did not improve the clinical primary end point, the ventilatory anaerobic threshold. However, in a pre-specified subgroup analysis consisting of about 50% of the overall population characterised by baseline ejection fraction ≥ 25% and NYHA class III, CCM did significantly improve the ventilatory anaerobic threshold as well as other parameters (peak VO2, Minnesota Living With Heart Failure Questionnaire and NYHA class).

The device and implantation procedure

Cardiac contractility modulation signals are delivered by a device (the OPTIMIZER, Impulse Dynamics, Or-

Figure 2

A. CCM OPTIMIZER IV generator B. External charger used to recharge the battery of the generator on a weekly basis C. Device programmer.

angeburg, NY), the only clinically available system to date. The device resembles and is implanted like a large pacemaker in a minimally invasive procedure, but does not have pacing or anti-tachycardia therapy capabilities. The OPTIMIZER IV System, the last version of the device (the main change being a reduction in size from 58cc to 29cc, fig. 2A) was CE-marked and introduced in Germany in April 2013. It consists of a pulse generator implanted in the subclavian region with a rechargeable lithium battery that delivers CCM signals and three commercially available pacing leads that are introduced under fluoroscopic guidance as for a standard pacemaker (fig. 3). One electrode is positioned in the right atrium and is used only for sensing atrial activity to synchronise the system to apply the pulses exclusively during sinus rhythm. The ventricular electrodes, used for both sensing local electrical activity and for CCM signal delivery, are placed on the right ventricular septum at least 2cm apart. System implantation is guided by measuring acute increase in left ventricular dP/dtmax. If initial lead placement does not result in at least a 5% increase in dP/dtmax

Figure 3

OPTIMIZER III system (implanted on the patient's right side) with a single-chamber ICD (implanted on the patient's left). Image reproduced with permission by Impulse Dynamics (Orangeburg, NY, USA).

within approximately 10 minutes of signal application, the electrodes are repositioned. An external charger (fig. 2B) is used by patients to recharge the battery transcutaneously at home once per week, which usually takes about 90 minutes. Finally, a programmer (fig. 2C) is used to interrogate and program the device as for a pacemaker.

Clinical perspective

Experimental data and small observational studies have shown encouraging results in term of safety and effectiveness of this therapy. However, in FIX-CHF 5, the largest randomised trial to date, the primary clinical end-point was not met in the overall population but was limited to a predefined sub-group. Therefore, further investigations are required before CCM can be accepted as a recommended treatment for heart failure patients in international guidelines.

Required supplementary investigation

Follow-up has been relatively limited in the trials to date, and long-term (>1 year) data on the effect of CCM are not available. Another limitation of the randomised trials is the absence of echocardiographic data analysing the impact of CCM on reverse remodelling. As results from FIX-5 suggest that benefit of the therapy seems to be limited to subsets of patients (baseline LVEF $\geq$25%), the target population that is most likely to respond to this therapy needs to be evaluated with randomised studies. There is currently no evidence that CCM reduces hard clinical endpoints such as mortality or hospitalisation. Ideally, studies should focus on patients who are not candidates or have limited response to cardiac resynchronisation therapy (e.g. narrow QRS, non-left bundle branch block, diastolic heart failure, right ventricular dysfunction etc.). Moreover, more research is probably required to determine the optimal pacing configuration (single or biphasic stimuli, delay from the pacing spike, duration of each phase and amplitude of the signal), the optimal daily duration of therapy application, and the optimal number and localisation of the pacing sites.
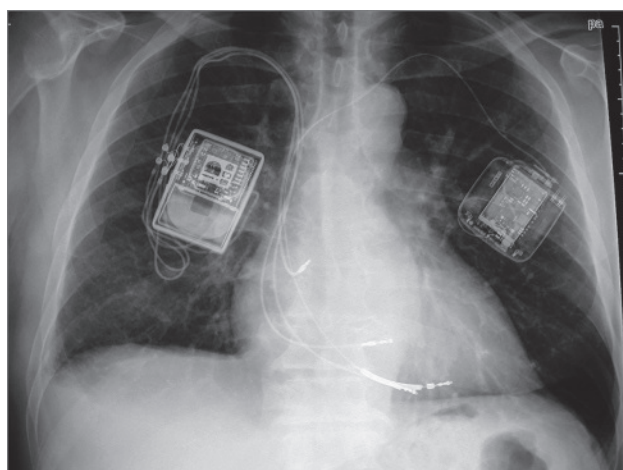
Required technical improvements

Different technical limitations need to be solved. With the last version of the device, CCM cannot be delivered to patients with atrial fibrillation or repeated ectopy since it is designed to inhibit CCM delivery on arrhythmias and relies on detection of a P-wave. A future device is supposed to incorporate an algorithm that does not rely on P-wave detection and therefore could be used in patients with atrial fibrillation. The development of a device combining CCM with ICD functions may be required in this population of heart failure patients. This would be facilitated by development of a single device that incorporates pacing, antitachycardia therapies and CCM. Finally, a simple method to guide lead positioning would be welcome. To date, an acute rise in invasive LV dP/dtmax is mandatory, without any demonstration of relation between acute haemodynamic and long term clinical response.

Introduction of CCM in Switzerland

Even though CCM is reimbursed in Switzerland, this was inherited from the German coding system (which is the only other country currently granting reimbursement for CCM), and did not undergo a formal technology assessment by the national healthcare authorities. The manufacturer has been promoting CCM in Switzerland, although to the best of our knowledge, no devices have been implanted to date.

Conclusions

Cardiac contractility modulation has been studied for more than 10 years as a treatment for heart failure. Non-excitatory pacing stimuli are delivered during the ventricular refractory period, which is believed to modulate intra-cellular calcium, and perhaps also to alter protein phosphorylation and gene expression which may improve cardiac pump function. Much of the data regarding this therapy has been experimental or observational, with a single medium-sized randomised study (FIX-CHF 5) that showed some promising results, albeit in subgroups of patients. Further data from large-scale randomised studies with long-term follow-up are required before this therapy may one day be recognised as valid treatment in international guidelines. In the meantime, compassionate use of CCM may be considered for patients not fulfilling criteria (e.g. narrow QRS) or not responding to CRT. Nevertheless, we would strongly advocate including these patients in an independent international registry, as clinical experience with CCM is limited.

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