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Cardiac contractility modulation (CCM) in chronic heart failure: mechanistic insights and clinical implications

Peysh A Patel

Take Home Messages
• The topic is important because CCM may offer a novel therapeutic option in patients with CHF who are ineligible for CRT. • This editorial provides an overview of physiological mechanisms and data from clinical trials. • Going forward, increased procedural familiarity and data on long-term outcomes shall inform clinical practice. • My opinion is that further mechanistic insights are warranted before CCM can be incorporated into routine practice.

Introduction

In patients with chronic heart failure (CHF) that have persistence of symptoms despite optimal medical therapy (OMT) and prolonged QRS duration, cardiac resynchronisation therapy (CRT) has been shown to improve symptoms and quality of life [1]. Significantly, it also reduces hospitalisations and confers mortality benefit [2]. However, around 30% of cohorts treated with CRT are confirmed to be non-responders [3]. In addition, 60% of heart failure sufferers have normal QRS duration [4], and benefits of CRT do not extend to those with normal or marginally increased QRS duration in whom outcomes may be worsened [5]. There is therefore the potential to diversify therapeutic options in this cohort.

What is the underlying physiology in CCM?

Cardiac contractility modulation (CCM) refers to electrical impulses delivered during the absolute refractory period (ARP) of the action potential, around 30ms after onset of QRS complex. It incorporates biphasic, bipolar signals administered for a duration of 20ms, with energy levels that are 50-100 fold that of a standard pacemaker impulse. They are typically administered for 5-12 hours on a daily basis. The shorter duration appears comparable in effectiveness [6], is more efficacious in reducing battery drain

and enables eligibility of patients with frequent ectopy burden who may otherwise be excluded.

Impulses do not elicit a new action potential and the electro-mechanical impulse is unaffected (i.e. 'non-excitatory'). Treatment has been shown to alter acute haemodynamics (contractility) as measured by dP/dt_{max}, but significantly, without a concurrent increase in myocardial oxygen consumption (MVO_2) [7]. This phenomenon is analogous with CRT whereby haemodynamic and clinical benefits are derived without augmenting energy requirements. Although the natural history of CHF relates to a gradual prolongation in QRS duration, it has been shown to remain constant during CCM albeit over a 2 year follow-up period [8].

The implantation procedure is in many ways comparable to that of a transvenous pacemaker system. CCM therapy is provided by a pacemaker-like generator (OPTIMIZER III, IMPULSE Dynamics) that is attached to two standard active fixation leads. These are placed along the mid-septal wall with an anatomical separation distance of at least 2cm. The proposed target zone are the septo-parietal trabeculations situated in the inferior portion of the septal right ventricular outflow tract (RVOT). Adequate sensing parameters are prioritised above the capture thresholds. A separate right atrial lead is positioned via active fixation to sequence with atrial activation.

What are the cellular mechanisms?

CCM exerts multiple effects at cellular and molecular levels, with acute benefits relating to alterations in calcium handling that enhance contractile performance. Both systolic and diastolic ventricular dysfunction are associated with alterations in cellular calcium homeostasis [9]. CCM has been shown to upregulate L-type calcium channels resulting in augmentation of intracellular calcium influx during the subsequent membrane depolarisation. There is also concurrent uptake into the sarcoplasmic reticulum via sarcoplasmic reticulum calcium-ATPase 2a (SERCA2a) receptors, thus improving calcium-triggered calcium release via ryanodine receptors (RyR2) [10]. Analysis of endomyocardial biopsies from subjects with CHF after 3 months has shown increased expression of SERCA2a and RyR2, suggesting that CCM therapy normalises defective

expression and reverts to the foetal gene programme [11]. These acute contractile effects are additive to those of CRT, as they arise from different mechanisms.

Animal models have shown that within minutes of signal delivery, there is a local shift in myocardial gene expression of key calcium cycling and stretch response components [12]. Interestingly, this alteration is also exhibited in remote sites such as the left ventricular free wall after chronic therapy [13]. This phenomenon may relate to diffuse changes in gene expression as a consequence of global effects on ventricular haemodynamics, or via direct transmission through gap junctions. Results broadly correlate with human studies using tissues derived from myocardial biopsies [14]. Importantly, this was associated with improvements in peak oxygen consumption (VO_2) and subjective assessment of quality of life (QoL) [11]. Data from animal studies also indicates that chronic CCM monotherapy increases left ventricular ejection fraction (LVEF) and reduces fibrotic burden [12], which may relate to normalised expression of matrix metalloproteinases [15].

What do clinical trials suggest?

FIX-HF3 was the first study to assess clinical effectiveness of CCM therapy, though it was unblinded and observational [16]. In patients with drug-refractory New York Heart Association (NYHA) class III CHF and narrow QRS duration, improvements were observed at 2 month follow-up in LVEF, 6-minute walk, NYHA functional class and QoL scores as measured by the Minnesota Living with Heart Failure Questionnaire (MLWHFQ). This was succeeded by the first, randomised, double-blinded crossover study in patients with severe left ventricular dysfunction (LVSD) quantified as LVEF < 35%, and NYHA class II/III (FIX-HF4) [17]. Peak VO_2 increased comparably in the two groups at 3 month follow-up, suggestive of a potential placebo effect, but there was a statistically significant improvement at the end of the treatment period (i.e. 6 months) which correlated with QoL assessment.

The FIX-HF5 study explored sicker cohorts (NYHA III/IV) for a 6 month period, though the study was unblinded due to ethical concerns [18]. It was the largest clinical trial of CCM to date, performed across 50 centres in the USA. The primary endpoint of

ventilatory anaerobic threshold (VAT) did not differ, though peak VO_2 and QoL scores were improved. Notably, the use of VAT as a measure of exercise tolerance is disputable as patients with CHF cannot typically exert themselves sufficiently to reach the required threshold for lactate production. An exploratory subgroup analysis observed significant treatment benefits in those with LVEF of 25-45% [19], which has been subsequently verified by a prospective, confirmatory RCT [20].

A meta-analysis in 2014 incorporated individual patient data from 3 studies and 641 participants [21]. Overall, CCM was suggested to exert modest yet statistically significant benefits on peak VO_2, 6-minute walk and QoL. This data is aligned with haemodynamic assessments of CCM therapy, with one study exhibiting an improvement in LVEF by 5% and reduction in end-diastolic volume (EDV) by 12mls after 3 months, suggestive of reverse remodelling [22]. This response is comparable to that of CRT in patients with mild QRS prolongation [23].

The effect of CCM on survival remains to be established. A case-control study with a 6 year follow-up period has shown a reduction in all-cause mortality, and particularly in subcohorts with LVEF of 25-40% [24]. Similar results have been presented from a retrospective study in cohorts with NYHA II/III symptoms, with mortality reductions at 1, 2 and 5 years when compared with predicted survival using the Seattle Heart Failure Model (SHFM) [25]. The CCM-REG registry has now provided long-term outcome data from a real-world perspective for up to 3 years, and results are suggestive of a sustainable impact of CCM on functional capacity, QoL and mortality [26].

What is the future of CCM?

European Society of Cardiology (ESC) guidelines for the treatment of CHF stipulate that "the evidence is considered insufficient to support specific guideline recommendations for CCM" [27]. However, it "may be considered in selected patients with CHF" and is approved for clinical use in some European Union (EU) countries, China, India, Australia and Brazil. Nonetheless, many uncertainties remain. The magnitude of derived haemodynamic benefit is likely to rely on precise septal positioning, which confers procedural complexity. It is unclear whether effects are dependent upon underlying

aetiology of cardiomyopathy, analogous to the DANISH trial that observed an absence of mortality benefit in patients with non-ischaemic CHF that received prophylactic implantable cardioverter-defibrillators (ICD) [28].

Around 25% of patients with CHF have co-existent atrial fibrillation, and those with permanent dysrhythmia may be challenging due to the loss of atrial sensing. However, newer versions of the device appear to incorporate algorithms to circumvent this limitation [29]. The role of CCM in patients with non-severe LVSD and preserved ejection fraction (HFpEF) is yet to be elucidated. However, preliminary studies in the latter group have suggested positive findings, which may relate to upregulation of the cardiac protein titin which is involved in early diastolic recoil and late distensibility of cardiomyocytes [30]. Lastly, a rigorous cost-benefit analysis of CCM therapy needs to be conducted. One economic evaluation has estimated gain in quality-adjusted life years (QALY) of 5.26 compared to 4.00 for OMT. This equates to a cost per QALY of around £16,000 which is comparable with the derived benefit from CRT/ICD devices and below the designated threshold of £20-30,000 utilised in the UK [31].

Final thoughts

In summary, CCM offers a novel therapeutic option for patients with symptomatic, severe CHF that are ineligible for CRT based on QRS duration. Early studies in both animals and humans suggest positive effects on myocardial dynamics and reversal of the typical maladaptive gene profile that exists in CHF. However, further mechanistic insights and clarification of effects on long-term morbidity and mortality are necessitated before CCM can be considered part of the routine device armamentarium to treat patients with CHF.

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