Modulation of cardiac contractility. A potential treatment of heart failure?

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This editorial refers to ‘Randomized, double-blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure’† by M.M. Borggrefe et al., on page 1019

During the last 10 years, electrical treatment of heart failure (HF) has become more and more popular. Cardiac resynchronization therapy (CRT), alone or combined with defibrillation, has been confirmed to be effective in patients with moderate or severe HF and ventricular dyssynchrony, manifest as a QRS duration >120 ms, though its effectiveness has not been confirmed in patients presenting with HF and a narrow QRS. As for all new treatments of HF, the clinical validation of CRT has been slow and occurred in four stages, including (i) limited observational studies to establish its feasibility; (ii) short-term, randomized, crossover studies to validate the clinical concept; (iii) large, controlled, parallel-design trials with a view to measure the clinical impact of this therapy on major morbidity and mortality; and (iv) publication of clinical guidelines. It took >10 years after the publication of the first case report for professional societies to assign CRT a Class I, evidence level A, indication.7

Borggrefe et al.8 report the results of a first, crossover, randomized study of large size, which examined the safety and efficacy of cardiac contractility modulation (CCM), a new form of electrical treatment of HF. As in the case of CRT, these are the initial stages of the clinical validation process.

CCM is an original and interesting concept, though its mode of action remains obscure.9–12 It is based on the delivery of electrical signals to the myocardium during the absolute refractory period. The ‘non-excitatory’ CCM impulse contains ~150 times the energy delivered by a conventional pacing pulse. In contrast to paired pacing, or to post-extrasystolic potentiation, CCM pulses do not induce additional action potential. While they do not cause contraction of the myocyte, studies in isolated, superfused, normal papillary muscle suggest that CCM pulses modify the entry of calcium into the cardiomyocyte and, consequently, its contractility.9 Subsequent short-term studies in animal models of chronic HF found that 6 h of CCM signals delivered to the left ventricular (LV) epicardium caused a mean 42% increase in LV ejection fraction (EF) and decrease in LV end-diastolic pressure, without increasing myocardial oxygen consumption. In long-term experiments, the improvement in LV function persisted for 3 months during application of CCM for 2–6 h daily. It is noteworthy that the effect was observed with CCM applied to the LV epicardium as well as to the right interventricular septum.9,10 Imai et al. recently reported that 3 months of CCM applied to the septum was associated with a significant decrease in LV volumes, consistent with reverse remodelling.12 No chronotropic or proarrhythmic effects, and no significant changes in QTc interval were observed. Additional data suggest that the improvement in LV systolic function and changes in LV dimensions could be due to changes in the sarcoplasmic reticulum and calcium cycling. Studies in normal dogs, as well as in dogs suffering from HF, showed a normalization of the sarcoplasmic reticulum calcium cycling proteins and gene expression by CCM applied in the absolute refractory period.10,12

Clinical experience with CCM

Clinical applications of CCM have, thus far, been few. In 2002, Pappone et al.13 described the immediate haemodynamic effects of the delivery of CCM signals via temporary endocardial electrodes in patients presenting with HF and a mean 28 ± 6% LVEF. They observed a 10% mean increase in maximum dP/dT during CCM application, an effect that was independent from baseline QRS duration, and appeared additive to biventricular stimulation when both were combined. Two years later, the same authors reported their initial experience with the long-term application of CCM in man. The implanted system was very similar to that used by Borggrefe et al.8 Three endocardial leads were implanted, including two, anterior and posterior, respectively, right ventricular septal leads to apply the CCM pulses to the myocardium, and one in the right atrium to synchronize the system and apply the pulses exclusively during sinus rhythm. Although the device is incapable of pacing or delivering antitachycardia therapy, it is compatible...
with an implanted pacemaker or cardioverter defibrillator (ICD). It was implanted in 23 patients in New York Heart Association (NYHA) HF class III, whose mean age was 62 years, mean LVEF 22 ± 7%, and QRS width ≥ 120 ms, followed for 2 months. To spare the battery, CCM was delivered for 2–3 h/day. Because of its high energy consumption, the average longevity in that device was limited to 6–8 months. Within the limit of the 2-month follow-up, no major adverse event was observed, in particular no pro-arrhythmia.

Neelagaru et al. recently published the results of a randomized, double-blind crossover study comparing the functional effects of CCM activated for 5 h/day, vs no CCM, during two 6-month periods each. They studied 49 patients in NYHA HF classes III or IV, whose mean age was 56 years and mean LVEF 28%. No statistically significant difference was observed between CRT ON and CRT OFF with respect to NYHA class, exercise capacity, or quality of life. These neutral results might be partially explained by a non-balanced distribution of the main baseline characteristics between the two randomized populations.

The study by Borggreffe et al. is similar to that by Neelagaru et al. They included patients in NYHA HF functional class III or IV, with an LVEF < 35%, not candidates for CRT, but it is noteworthy that the mean QRS duration of the population was 118 ± 27 ms, near the 120 ms cut-off recommended for indication for CRT. Inclusion in the study occurred after a test of CCM applied via septal leads, which showed a ≥ 5% increase in dp/dt max. This selection of potential responders excluded 6.7% of patients who did not satisfy this entry criterion. The study design was identical to that of the MUSTIC trial, which, in 2001, was the first to establish the clinical efficacy of CRT in patients with HF and a wide QRS. The crossover phase included two periods of 3 months each. During the period of CRT, CCM pulses were applied for a total of 7 h/day. The study objectives were mainly functional, including a combined primary endpoint of exercise capacity (peak VO₂) and quality of life. Compared with the study by Neelagaru et al., this study included a 3-fold greater number of patients (n = 164), and had a properly balanced proportion of baseline characteristics between the two randomized groups. With respect to clinical efficacy, a weak, though statistically significant difference was observed in favour of CCM ON for the combined primary end-point and for each of its components. A similar trend was observed for the distance covered during a 6 min walk. While, in a 2 × 2 crossover trial, it might be improper to analyse differences between treatments in each phase separately, it is noteworthy that a significant difference between the two treatments was observed only in the second crossover period, with no apparent difference in the first phase, an observation strongly dissimilar from that made in MUSTIC, where the difference between the two study arms was evident in the first phase, and confirmed by an inversion of the curves in the second phase. Besides these methodological reservations, one might also underline that the difference observed during the second crossover period was mainly due to worsening of the measurements made between CRT ON and CRT OFF, while they remained stable at 3 and 6 months in the arm assigned to CRT OFF followed by CRT ON. It is, therefore, difficult to distinguish a therapeutic effect conferred by CCM from a carryover effect.

Other limitations of this study include the absence of serial measurements of LV dimensions, which might have allowed the detection of reverse remodelling by CCM, as was observed previously in a canine study. Repeated measures of LVEF, available in only 50% of patients, showed no difference between CCM ON and CCM OFF. Furthermore, the influence of ischaemic vs non-ischaemic heart disease on the clinical efficacy of CCM remains unknown. Finally, because of its design and short duration, this study does not contribute information with respect to HF-related morbidity and overall mortality. This preliminary report allows the drawing of no firm conclusion regarding the clinical merits of this new technique, which appears relatively safe.

Technical considerations

If it can be clinically validated, the development of this therapy will need to overcome unresolved technical difficulties, which are not brought up in this article. For instance, it will need to determine (i) the optimal position of the ventricular leads that apply CCM; (ii) the optimal daily duration of application; and (iii) whether the application must be continuous or intermittent. Since the energy consumed by CCM pulses is high, the battery life in the original device was limited to 6–8 months. The need for frequent replacements of the pulse generator would be a major limitation of this therapy, which might be partially resolved by batteries that are rechargeable transcutaneously. Other technical limitations include the absence, currently, of an algorithm allowing the safe delivery of CCM during atrial fibrillation, and the absence of a device combining CCM with other therapies widely used in chronic HF, such as CRT and ICD. A large proportion of candidates for CCM have an approved indication for ICD. Currently, they would have to undergo the implantation of two different devices, each with its own set of leads!

In conclusion, further investigation and technical improvement are required before CCM can be regarded as a treatment of HF.

Conflict of interest: none declared.

References


