Cardiac contractility modulation by non-excitatory electrical currents. The new frontier for electrical therapy of heart failure

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Background

Heart failure (HF) may complicate ischemic heart disease in both its acute and chronic manifestations, representing a prevalent health problem throughout the world. Development of therapies to improve heart function, relieve symptoms, reduce hospitalizations and improve survival is a high priority in cardiovascular medicine. The available pharmacological strategies, including angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, beta-blockers, and aldosterone receptor antagonists have recently been complemented by new electrical therapy, including implantable cardioverter-defibrillators for “MADIT II” patients and cardiac resynchronization for the 30% of HF patients with concomitant intraventricular conduction delay.

The wide variety of available HF medications provides ample evidence that we have not yet succeeded in this effort. Safe and effective inotropic electrical therapy could be a useful addition to our therapeutic armamentarium in an attempt to correct Ca²⁺ fluxes abnormalities during the cardiac action potential.

Cardiac contractility modulation (CCM) by means of non-excitatory electrical currents delivered during the action potential plateau has been shown to acutely enhance systolic function in humans with HF. Herewith, we report on our preliminary experience with CCM therapy for patients with HF, providing fundamental notions to characterize the rationale of this novel form of therapy.

Briefly, CCM therapy appears to be safe and feasible. Proarrhythmic effects of this novel therapy seem unlikely. Preliminary data indicate that CCM gradually and significantly improves systolic performance, symptoms and functional status. The technique would appear to be attractive as an additive treatment for severe HF. Controlled randomized studies are needed to validate this novel concept.

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cycle, the ryanodine receptor, the sarcoplasmic reticulum Ca\textsuperscript{2+} ATPase, and the phospholamban, with progressive reduction as the failing heart deteriorates\textsuperscript{5,7}. On the contrary, both L-type Ca\textsuperscript{2+} channel and the Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger, mediating the voltage-dependent extracellular Ca\textsuperscript{2+} cycle, are increased in the failing ventricle. Overall, these changes fit the pattern of “reversion to fetal phenotype” of the excitation-contraction coupling, with a poorly developed sarcoplasmic reticulum and a shift from intracellular to extracellular Ca\textsuperscript{2+} cycle\textsuperscript{8-10}.

**Inotropic effects of electrical currents.** On this background, a theoretical possibility exists to modulate Ca\textsuperscript{2+} handling through the extracellular Ca\textsuperscript{2+} cycle by affecting the magnitude and duration of the cardiac action potential. From a historical perspective, minor changes in membrane potential during the absolute refractory period by passing small currents through an intracellular electrode, as a mean to modulate cardiac contractility, have been investigated by Wood et al.\textsuperscript{11} in 1969. Briefly, their findings reflect the ability of the small currents applied during the action potential plateau to modify the open state of the plasma membrane Ca\textsuperscript{2+} channels so as to increase the entering of this activator of cardiac contraction.

**Extracellular, field “stimulation”.** As intracellular currents clearly cannot be delivered in the intact heart, investigation of this type of approach as a potential therapy for patients with HF has been undertaken only recently. Indeed, a conceptual breakthrough occurred, with the recognition that similar effects can be achieved with field stimulation of myocardial tissue\textsuperscript{12}.

Burkhoff et al.\textsuperscript{13} have investigated the effects of square-wave current pulses applied during the absolute refractory period of action potential generated by a pacing stimulus in isolated, superfused, isometrically contracting rabbit papillary muscle. These signals, referred to as cardiac contractility modulation (CCM) signals, are timed just as to fall immediately before the peak of developed tension, as it has been shown that currents applied in this narrow window after the beginning of action potential, exert an inotropic effect not inferior to subthreshold currents maintained during the entire cardiac cycle\textsuperscript{11}. Intracellular recordings at steady state (Fig. 1) show that CCM signals induce an increase in action potential duration that correlate to CCM amplitude\textsuperscript{13}. Conceivably, the increased duration of the action potential allows for an increased influx of Ca\textsuperscript{2+} paralleled by an increased peak tension.

**Cardiac contractility modulation signal effects on Ca\textsuperscript{2+} transient.** The hypothesis that intracellular and extracellular currents could modulate cardiac contractility by influencing Ca\textsuperscript{2+} cycling has been directly tested; by means of aequorin injection into the cardiac muscle, [Ca\textsuperscript{2+}], may be estimated during CCM signal application. As shown in figure 2, CCM signal signifi-

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**Figure 1.** Isometric force (top) and transmembrane action potential (bottom) recordings under steady-state baseline conditions and under steady-state conditions during cardiac contractility modulation (CCM) treatment with two different amplitude settings. The increase in contractile force generation is accompanied by an increase of the action potential duration. In the inset, the red bar represents the phase of the cardiac action potential (just prior to the peak tension development) critical for modulating contractility by using electrical currents.

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significantly increased both peak [Ca\textsuperscript{2+}] and isometric force, confirming that the mechanism by which CCM signal enhances contractility involves increasing Ca\textsuperscript{2+} delivery to the myofilaments\textsuperscript{13}.

Regional versus global cardiac contractility modulation. Extracellular electrical fields applied to small size muscle preparations are likely to reach and affect function of a large proportion of myocytes. However, in vivo field stimulation of the entire hearts of larger mammals is not feasible because of practical considerations related to power availability. Thus, the hypothesis was successfully tested that contractile strength of the entire heart can be significantly enhanced by CCM application to a region of the heart\textsuperscript{13,14}.

Summary.
- It has been previously recognized that cardiac contractility can be modulated by actively controlling the duration and profile of the action potential by means of intracellularly delivered and electrotonically conducted currents, which in turn influence Ca\textsuperscript{2+} entry\textsuperscript{8}.
- The application of extracellular electrical fields during the refractory period can exert similar effects on action potential, Ca\textsuperscript{2+} cycling and contractility in vitro\textsuperscript{12,13}.
- The mechanisms could therefore involve increased transsarcolemmal Ca\textsuperscript{2+} fluxes through L-type Ca\textsuperscript{2+} channel, with an indirect effect mediated by the increased sarcoplasmic Ca\textsuperscript{2+} loading mediated by the sarcoplasmic reticulum Ca\textsuperscript{2+} ATPase\textsuperscript{12,13}.
- Although the sarcoplasmic reticulum function is known to be depressed in HF, CCM signals increase contractility in this setting, likely prolonging the reverse-mode Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger-mediated Ca\textsuperscript{2+} influx and decreasing Ca\textsuperscript{2+} efflux through inward Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger as an adjunctive mechanism\textsuperscript{10,12,13,15-17}.
- In vivo regional application of CCM can exert significant global inotropic effects, as a direct result of more dramatic changes in regional contractility close to the CCM stimulation site\textsuperscript{14,18}.

Clinical studies
First acute hemodynamic human study. Pappone et al.\textsuperscript{19} first evaluated the feasibility of CCM stimulation in patients with chronic left ventricular systolic dysfunction due to ischemic cardiomyopathy. To obtain insight into potential mechanisms relevant to clinical application, this study has explored the influence of varying CCM delivery ventricular chamber on hemodynamic and mechanical response, and has evaluated the potential independent effect of altering myocyte function by CCM while enhancing contractile synchrony by simultaneous cardiac resynchronization therapy in HF patients with complete left bundle branch block.

This study included patients with either ischemic or idiopathic dilated cardiomyopathy with an ejection fraction < 35%. By design, CCM stimulation is non-excitatory and needs to be delivered within a precise time window of local refractoriness determined by local electrical myocardial activation sensing. Such CCM signals are produced through a line-powered device equipped with a waveform generator triggered by local activation. The CCM current used was a biphasic, square-wave pulse 20-40 ms in duration, delivered 30-60 ms after detection of local activation.

There were three study protocols. In protocol 1, CCM signals were delivered to the left ventricle. In protocol 2, CCM signals were applied to the right ventricular septum. In protocol 3, performed in HF patients with complete left bundle branch block and left ventricular end-diastolic diameter > 55 mm, CCM was delivered to the left ventricle during simultaneous biventricular pacing performed from the same site to which CCM was applied using the setting configuration of protocol 1.

Hemodynamic measurements at steady state can be so summarized:
- the CCM signals were shown to induce a 9% increase in dP/dt\textsubscript{max} and a 10% rise in aortic pulse pressure during epicardial delivery to the left ventricle (Fig. 3);
- comparable systolic enhancement was also obtained by applying the CCM current to the right ventricular septum, raising the possibility that direct stimulation of the right ventricle may not be necessary to achieve significant benefits. In addition, the fact that we had no cases of chest discomfort with endocardial CCM application suggests that the right-sided approach may permit use of higher current amplitudes, which have been shown to correlate with stronger contractile potentiation in experimental preparations;
- quantitative echocardiographic analysis demonstrated a profound increase in regional contractility close to the site of CCM delivery (Fig. 4). Given the non-excitato-
ry nature of CCM, contractile enhancement in nearby segments which are effectively not stimulated is probably due to local unloading or stretching phenomena (Frank-Starling mechanism; Fig. 4);
• finally, CCM therapy synergizes with cardiac resynchronization therapy, whereas no evidence of decreased lusitropy due to Ca\(^{2+}\) overloading emerged (Fig. 5).

**First chronic human experience.** After extensive preclinical testing\(^9\) and assessment of acute hemodynamic efficacy in human beings\(^9\), we have prospectively conducted a treatment-only clinical pilot study to assess mid-term safety and preliminary efficacy of chronically implanted generators of CCM signals in patients with chronic systolic HF.

**Study protocol.** In this our preliminary experience we enrolled 13 patients, all of male sex. Age averaged 63 ± 9 years. The cause of HF was ischemic heart disease in 8 patients, idiopathic dilated cardiomyopathy in the remaining 5 patients. Mean left ventricular ejection fraction was 23 ± 7% at a mean heart rate of 73 ± 15 b/min. The characteristics of the study population are summarized in table I.

The OPTIMIZER II\(\text{TM}\) device for chronic CCM delivery was implanted upon evidence of ΔdP/dt\(_{\text{max}}\) ≥ 5% on hemodynamic acute testing; essentially, this device

Figure 3. Simultaneous recordings of left ventricular (LVP), dP/dt and aortic (AoP) pressures, with cardiac contractility modulation (CCM) therapy off (control) and on (CCM).

Figure 4. An example of end-systolic color kinesis images and segmental analyses acquired from a patient with left ventricular dysfunction at baseline (A and B) and during cardiac contractility modulation signal application (C and D). During cardiac contractility modulation signal delivery, wall motion improved not only in the hypokinetic segments in the apical septum and apical lateral walls near where the cardiac contractility modulation signal was applied, but also in remote regions (note different scale in panels B and D). A-lt = apical-lateral; A-sp = apical-septal; B-lt = basal-lateral; B-sp = basal-septal; M-lt = mid-lateral; M-sp = mid-septal; REDA = regional end-diastolic area; RFAC = regional incremental fractional area change.
is capable of monitoring cardiac electrical activity in both the right atrium and in the interventricular septum, of recognizing local activation and then of automatically delivering non-excitatory CCM signals at preset times and for predetermined periods of time.

The CCM signal resembles pacing signals in that it is characterized by a delay, a duration and an amplitude. A commercially available right atrial lead, used to record electrical signals from the right atrium, was placed high in the right atrium. Two commercially available right ventricular bipolar 8F electrocatheters were screwed in to the right aspect of the interventricular septum, with CCM currents delivered to the right aspect of the interventricular septum from the lead tip to the ring electrode.

Thereafter, follow-up started, with an 8-week period (FIX HF-3 substudy), in which CCM therapy was administered 3 hours a day between 7:00 and 10:00 p.m. and a 24-week phase (FIX HF-3 Extension substudy) in which CCM was applied 7 hours per day during 7 equally-spaced 1-hour periods, with the rationale of dose ranging for the effects of CCM therapy in terms of safety and efficacy.

Primary clinical endpoints were changes in left ventricular ejection fraction, peak oxygen uptake, and distance walked in 6 min. The safety endpoints were the evaluation of the proarrhythmic potential of the CCM signals and device-related adverse events.

Preliminary efficacy. The left ventricular ejection fraction increased and the end-diastolic and end-systolic dimensions decreased at the end of each study phases as compared with pre-implant (p < 0.05 for all comparisons). The left ventricular ejection fraction increased from 23 ± 7 to 28 ± 7% at the end of the FIX HF-3 phase (p < 0.05 for comparison with baseline), with a further significant increase to 35% at the end of the FIX HF-3 Extension phase (p < 0.05 for comparison with baseline and p < 0.05 for comparison with the previous FIX HF-3 phase, after Bonferroni adjustment for multiple pairwise comparisons).

Not significant changes were found in parameters of diastolic function, either considering isovolumic relaxation time or the pattern of mitral inflow, including Doppler early diastolic filling velocity and atrial velocity filling, their ratio and early deceleration time.

Peak myocardial oxygen consumption, parameter of maximal exercising, gradually and significantly improved when comparing baseline, 3- and 7-hour phases (overall, p < 0.05; Table II).

Table I. Baseline clinical characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Age (years)</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Distance walked in 6 min (m)</td>
<td>408 ± 110</td>
</tr>
<tr>
<td>Peak O2 uptake (ml/kg of body weight/min)</td>
<td>13.8 ± 1.1</td>
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<tr>
<td>Quality of life score*</td>
<td>36 ± 21</td>
</tr>
<tr>
<td>QRS interval (ms)</td>
<td>107 ± 22</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>23 ± 7</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>13/13</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>12/13</td>
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<tr>
<td>Spironolactone</td>
<td>6/13</td>
</tr>
<tr>
<td>Digoxin</td>
<td>7/13</td>
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<tr>
<td>Diuretics</td>
<td>11/13</td>
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LV = left ventricular. * a higher score indicates a poorer quality of life (range 0 to 105).
During the FIX HF-3 phase the mean distance walked in 6 min was 14% longer as compared with baseline, with a further 19% increase at the end of the FIX HF-3 Extension phase (p < 0.05). Indeed, the mean distance walked in 6 min (418 ± 71 m at baseline) increased of 59 m (477 ± 72 m, p < 0.05) and 80 m (498 ± 92 m, p < 0.05) at the end of each phase as compared with baseline.

**Safety.** By serial Holter ECG recordings, we analyzed the impact of CCM therapy on the amount of ventricular and supraventricular arrhythmias. By generalized linear model for repeated measure analysis, we found no significant trend over time toward an increase in the mean number of premature ventricular or supraventricular complexes per day. A similar decrease was observed in the number of non-sustained ventricular tachycardia per day across the study phases (p = 0.01). No significant changes in the duration of the QRS interval or QT interval were observed across the entire study.

Although the device was indeed replaced in all patients after a mean of 7 ± 3 months, only 1 patient experienced a pocket infection after the device had been replaced that was successfully treated with local measures and antibiotics. In 1 patient the output was lowered by approximately 2 V because of symptoms from pocket stimulation, whereas phrenic stimulation prompted right ventricular lead repositioning in another patient.

**Discussion.** The criteria for entry into this pilot clinical study were stringent. The initial subjects had to be highly symptomatic despite a full medical therapy, encompassing diuretics, digoxin, angiotensin-converting enzyme inhibitors and in most cases beta-blockers. Nevertheless, to date all patients are alive, with only 2 patients who required HF-related hospitalization during a mean follow-up of 36 weeks.

Our findings parallel those of several trials reporting on morbidity and mortality in patients with HF20-25. The left ventricular ejection fraction gradually increased during follow-up, as did the distance walked in 6 min and the parameters of maximal exercise tolerance. The increase in left ventricular ejection fraction raised from a decrease in both the left ventricular end-systolic and end-diastolic volumes, without a significant increase in the stroke volume. These findings are compatible with the hypothesis that CCM signal application may affect cardiac contractility by a primary effect on the left ventricular end-systolic pressure-volume relationship, as also shown in animal models14,26, with secondary effects on the reduction of end-diastolic volume. In keeping with these findings are the results of the diuretic agent usage that declined during follow-up. This may reflect the above-mentioned progressive reverse cardiac remodeling, with reduced cardiac volumes and pressures, and reduced symptoms of congestion. Of note, the graded increase in left ventricular ejection fraction between the two study phases was paralleled by changes in several parameters of functional capacity.

The procedure was well tolerated, with an overall implant procedure duration not different from that for standard dual-chambered pacemaker and inferior to that reported for implantation of biventricular pacemakers23-25. Implantation of the atrial lead and of the two right ventricular leads was attempted in all patients, with a 100% success rate.

We had no evidence of increased ventricular irritability due to CCM signal delivery on the QRS complex after implantation and during follow-up. Furthermore the increase in Ca2+ cycling due to CCM delivery did not impact any parameter of diastolic function we evaluated during follow-up.

The probability of adverse events directly and indirectly related to the device, was quite low and accept-
able for a device implant procedure, with only 1 patient who experienced a pocket infection after the device had been replaced, although the device was replaced in 12 out of 13 patients.

**Short-term inotropic therapy.** Chronic inotropic drug therapies for HF have been shown to worsen survival and increase the need for hospitalization\(^2\). This has been postulated to be due to detrimental effects of continual beta-adrenergic pathway stimulation (by beta-agonists and phosphodiesterase inhibitors), which worsens myocardial contractility, induces arrhythmias, and has potentially unfavorable systemic effects. Intermittent, short-term intravenous inotropic therapy, on the other hand, is commonly employed to treat HF exacerbations. It is envisioned that CCM signals could be delivered therapeutically via a pacemaker-like device in a manner akin to intermittent short-term inotropic therapy. They could be delivered for relatively short periods of time (e.g., hours per day). Some of the detrimental of continuous intravenous inotropic therapies have also been attributed to systemic side effects. CCM signals have local myocardial effects and are devoid of systemic hemodynamic effects as suggested by the findings by Mohry et al.\(^1\).

**Limitations.** Although considerable additional work is needed to perfect the therapeutic capability of this device, it is a potentially important contribution that allows improving symptomatic and functional status in HF patients in whom survival but not quality of life benefits are provided by HF medications. However, further attention should be given to a number of questions about the use of CCM.

The present need for frequent generator replacement is also a limitation. Within the end of the study, the probability of infection of the CCM system generator was 4% as Li\(^+\) batteries provide a projected life of approximately 6-9 months.

Some of these questions can be answered only by further development and time, but they will probably determine the ultimate success of this approach. Further studies are justifiable because the potential benefits of using the device outweigh the risks to participating subjects.

**Conclusions.** Although these preliminary results support the validity of the assumptions on which the device is based and confirm preclinical and acute human results, we do not intend to suggest that most of the problems related to clinical implementation of this approach are solved. For example the requirement for frequent generator replacement due to battery depletion represents a distinct but, we hope, a temporary drawback. Increased ventricular irritability and or proarhythmia after implantation of the device, although not observed in our patients or in previous animal or human studies, is a theoretical possibility. It is important to remember, moreover, that OPTIMIZER II\(^TM\), like other cardiac devices, could malfunction because of failure of a component, battery depletion, improper sensing or CCM delivery, or case or lead fracture.

It is important to emphasize that the CCM therapy will not be a definitive treatment for HF and should not be regarded as a substitute for standard HF medical therapy or other electrical therapy. These approaches should be viewed as complementary rather than exclusive. In view of the increasing survival of HF patients, including many who are treated with beta-blockers but do not tolerate full doses, the demonstrated effectiveness of the CCM has important clinical implications. Although there is a clear need for additional information, our preliminary results are encouraging. If further studies provide evidence of long-term safety and reliability, CCM could become useful to symptomatic drug-refractory HF patients or to patients not tolerating symptomatic and functional effects of standard medical therapy.

**Riassunto**

La sindrome dell’insufficienza cardiaca può complicare il decorso della cardiopatia ischemica nelle sue manifestazioni acute e croniche. Dunque, lo sviluppo di approcci terapeutici finalizzati al miglioramento della funzione cardiaca, della sintomatologia, della morbilità e mortalità per pazienti con insufficienza cardiaca postischemica rappresenta una priorità nel settore cardiovascolare.

Agli attuali approcci farmacologici all’insufficienza cardiaca, mirati ad antagonizzare l’attivazione neurormonale caratteristica di questa sindrome, si sono recentemente aggiunti approcci di tipo “elettrico”. Questi ultimi permettono il trattamento delle aritmie ventricolari attraverso l’impianto di dispositivi antitachicardici in pazienti di tipo “MADIT II” e la resincronizzazione meccanica del ventricolo sinistro in un sottogruppo di pazienti con evidenza elettrocardiografica di dissincronia.

Se la terapia inotropa di tipo farmacologico è stata relegata al trattamento delle esacerbazioni dell’insufficienza cardiaca, nuovi approcci per modulare la contrattilità del ventricolo sinistro mediante terapia elettrica sono in fase di sperimentazione.

Riportiamo, quindi, la nostra esperienza preliminare sull’uso di un dispositivo in grado di erogare impulsi elettrici non stimolatori, modulanti la durata e l’ampiezza del potenziale d’azione cardiaco. Tali segnali elettrici denominati segnali CCM (cardiac contractility modulation) vengono erogati durante il periodo refrattario assoluto sul versante destro del setto interventricolare. Il razionale consiste nell’incremento dei flussi di calcio transmembrana attraverso i canali del calcio di tipo L, con successivo incremento dei depositi di calcio attivatore nel reticolo sarcoplasmatico. Questo tipo di
approccio, in parte echeggiante il concetto di potenzia-
mento postextrasistolico, è stato valutato acutamente
con successo nel nostro laboratorio e successivamente
13 pazienti sono stati impiantati con un dispositivo in
grado di erogare tali impulsi per una durata > 6 mesi. La
somministrazione di questo tipo di terapia per 3 ore al
giorno ha indotto un miglioramento dei parametri di
funzione sistolica del ventricolo sinistro, senza alterare
la funzione diastolica, né inducendo alcun effetto pro-
aritmico. La capacità funzionale e la qualità di vita dei
pazienti sono parallelamente migliorate. Un ulteriore
beneficio si è dimostrato erogando la terapia per 7 ore
giorno, con tuttavia una maggiore variabilità interpa-
ziente.

In conclusione, questo innovativo approccio si è di-
mostrato in via preliminare sicuro, e studi in corso su
una più ampia casistica permetteranno di confermare
anche la sua efficacia.

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