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Clinical research

Chronic electrical stimulation during the absolute refractory period of the myocardium improves severe heart failure

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KEYWORDS
Heart failure;
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Aim In experimental studies, nonexcitatory electrical stimulation delivered at the time of absolute myocardial refractoriness resulted in cardiac contractility modulation (CCM) with improved systolic function. This study reports the initial experience with CCM in patients with chronic heart failure.

Methods and results Twenty-five patients, 23 males, with a mean age of 62 ± 9 years and drug-refractory NYHA class III heart failure were assigned to CCM-generator implantation. The underlying heart disease was idiopathic dilated cardiomyopathy in 12 patients and coronary heart disease in 13 patients. Acute efficacy of CCM with 7.73-V stimuli delivered via two right ventricular leads was evaluated by measuring the time derivative of left ventricular pressure (dP/dt). After implantation, the CCM generator was activated for 3 h daily over 8 weeks.

In 23/25 patients the CCM system was implanted successfully. Heart failure significantly improved from NYHA class III to class II in 15 patients and to class I in 4 patients ($p < 0.000001$), left ventricular ejection fraction improved from $22 \pm 7\%$ to $28 \pm 8\%$ ($p = 0.0002$), and the Minnesota Living with Heart Failure Score improved from 43 ± 22 to 25 ± 18 ($p = 0.001$). The 6-min walk test increased from 411 ± 86 to 465 ± 81 m ($p = 0.02$). Nine patients (39%) had intermittent sensations associated with CCM delivery. There were two (8%) non-device-related deaths during follow-up.

Conclusions These preliminary data indicate that CCM by delivery of intermittent nonexcitatory electrical stimuli is a promising technique for improving ventricular systolic function and symptoms in patients with drug-refractory NYHA class III heart failure.

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Introduction

Experimental studies indicate that nonexcitatory electrical stimuli delivered during the absolute refractory period may modulate cardiac contractility.[1–3] When these cardiac contractility-modulating (CCM) signals were applied to rabbit papillary muscle, the force of contraction increased significantly.[2] This phenomenon was reproducible in trabaeculae obtained from human hearts explanted from patients with severe heart failure.[2] Experiments on these trabaeculae and isovolumically contracting, Langendorff-perfused ferret hearts suggested that electrically induced prolongation of the duration of the action potential with increased calcium delivery to myofilaments is one of the underlying mechanisms of enhanced cardiac contractility during CCM stimulation.[2,3]

The aim of this study was to evaluate the feasibility, safety, and efficacy of chronically implanted CCM generators in patients with severe chronic heart failure who are already on optimised medical therapy.

Methods

Patients with drug-refractory NYHA class III heart failure and ejection fraction $\leqslant 35\%$ were included. The patients had to be on optimised medical treatment for at least 4 weeks before study enrolment. In order to exclude potential candidates for biventricular pacing, all patients had to be in sinus rhythm with QRS complexes <140 ms.

In the CCM device used for chronic therapy in this study, built-in safety-designed algorithms inhibit the generation of CCM signals when any irregular electrical activity is detected, such as premature atrial or ventricular complexes, atrial fibrillation, or sensing defects. Therefore, this system includes an atrial lead in addition to two right ventricular leads. To achieve a substantial number of QRS complexes suitable for stimulation during the absolute refractory period, a maximum of 8900 ventricular ectopic beats per 24 h, monitored over a period of 4 days, was allowed. Subjects with documented sustained ventricular tachycardia and patients scheduled for, or who had undergone, revascularisation within three months of enrolment were excluded.

Written, informed consent was obtained from all patients. The study was approved by the respective Ethics Committees of the participating hospitals and carried out in compliance with the Declaration of Helsinki.

The CCM signal generator (Optimizer™ II, Impulse Dynamics, New Jersey, USA) used in this study is an implantable system that delivers two biphasic, square-wave signals of up to 7.73 V during the absolute refractory period (Fig. 1). The implanted system does not produce any kind of conventional single or dual-chamber pacing. Two commercially available pacemaker leads were used for sensing right ventricular activity and delivery of CCM signals (Tendril DX1388T-58, St. Jude Medical, St. Paul, USA). Another commercially available right atrial lead was used to record electrical signals from the right atrium (4068-52, Medtronic Inc, Minneapolis, USA) (Fig. 2).

The following parameters were evaluated during the 8-week follow-up period (Fig. 3): NYHA classification, Minnesota Living with Heart Failure Score, ventricular ectopic activity (48 h of

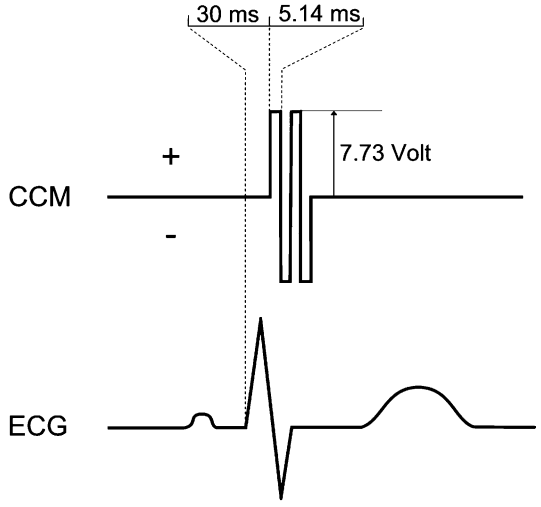

Fig. 1 Cardiac contractility modulation (CCM): two biphasic square-wave impulses of 7.73 V with 5.14 ms/phase, delivered 30 ms after the local myocardial activation during the absolute refractory period.

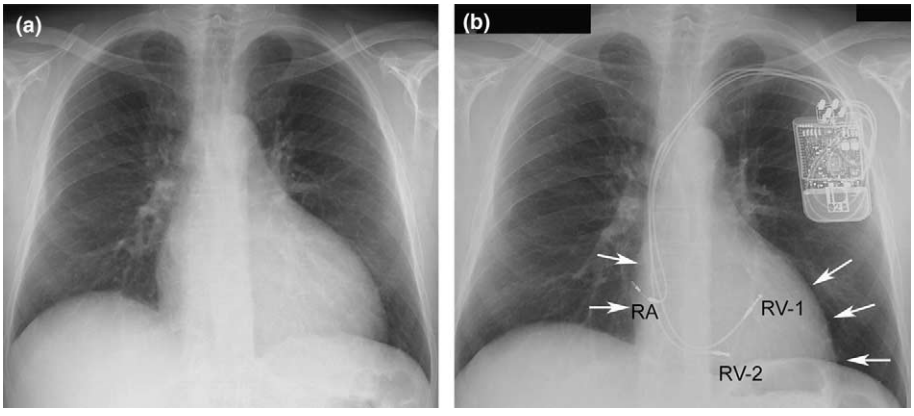

Fig. 2 (a) Chest X-Ray of a patient with NYHA class-III heart failure one day before implantation of the system for cardiac contractility modulation (CCM). (b) Substantial improvement of cardiothoracic ratio after 8 weeks of CCM therapy (arrows); two right ventricular septal leads (RV-1 and RV-2) for delivery of CCM stimulation, one right atrial (RA) lead for sensing atrial activity.

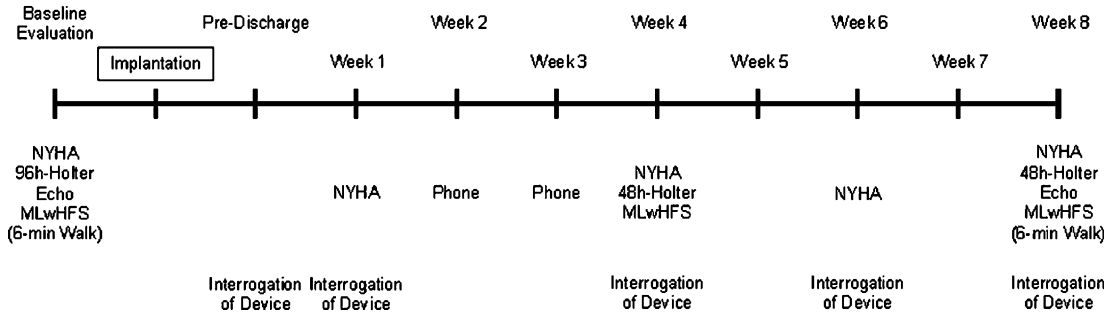

Fig. 3 Time-table of the study.

Holter monitoring), and CCM-associated symptoms. The Minnesota Living with Heart Failure Score is evaluated by means of a 21-item, self-administered questionnaire,[4] which determines the subjects' self-assessment of the impact of heart failure on their lives. The score ranges from 0 to 105, with a better quality of life indicated by lower scores. Left ventricular ejection fraction, which was the primary endpoint of interest, was measured echocardiographically at baseline and at least 12 h after the last CCM stimulation sequence during follow-up. Biplanar left ventricular end-diastolic and end-systolic cavity volumes were calculated using Simpson's rule[5] from paired apical four-chamber and apical long-axis echocardiographic images of a minimum of three cardiac cycles; mean values of each variable were estimated. Biplanar ejection fractions were calculated as $(\text{End-diastolic volume} - \text{End-systolic volume}/\text{End-diastolic volume}) \times (100\%)$.[6] The 6-min walk tests were performed randomly during working hours at baseline and during follow-up of CCM stimulation. Patients were instructed to walk as far as possible in 6 min on a 50-m course, with standardised encouragement and breaks as necessary. The track is marked at 0.5-m intervals throughout its length so that the distance walked can be accurately determined. The time elapsed was measured with a stopwatch and the distance walked was measured to the nearest meter. The outcome measure was the total distance walked in 6 min.

Device implantation was performed using a routine pacemaker-like approach. Additionally, the right or left femoral artery was cannulated for left ventricular catheterisation and measurement of the time derivative of pressure (dP/dt) (SPC-350 Mikro-Tip Catheter Transducer, Millar Instruments, Houston, USA and MegaPac Computer, Dolch, Fremont, USA). A bipolar lead was placed in the right atrium for sensing atrial activity, and two active fixation leads were placed on the anterior and inferior aspect of the mid-right ventricular septum for sensing ventricular activity and delivery of CCM signals. Right ventricular leads were positioned to deliver the stimulating electrical current to as much viable left ventricular myocardium as possible.

On signal delivery during the absolute effective refractory period via both right ventricular leads, left ventricular pressure measurements were made simultaneously and dP/dt was derived. A minimum increase in dP/dt of 5% was required for device implantation. In case of an insufficient increase in dP/dt with the initial lead configuration, one or both right ventricular leads were positioned differently and stimulation was tested again. Every stimulation test via both right ventricular leads was counted as one right ventricular lead position. If, despite testing different lead positions, CCM stimulation failed to sufficiently increase dP/dt and/or maximum output testing resulted in phrenic nerve stimulation, device implantation was abandoned.

The patients were discharged with the devices programmed to deliver CCM signals for 3 h a day between 7 and 10 p.m. The time and duration of daily signal delivery were chosen arbitrarily, since there was no prior human experience available other than acute catheterisation laboratory tests. The patients did not know how their devices were programmed.

Descriptive statistics were calculated for all variables (means $\pm$ SD). Datasets were tested for normal distribution. For comparisons of outcome parameters between baseline and follow-up, the two-sided Friedman ANOVA test was used for NYHA classification, left ventricular ejection fraction, Minnesota Living with Heart Failure Score, and ventricular ectopic activity; no corrections were made for multiple testing in this feasibility study. The Wilcoxon matched-pairs test was used to compare the results of the 6-min walk test, which were log-normally distributed. A p value <0.05 was considered statistically significant.

Results

Twenty-five patients, 23 males and 2 females, with a mean age of 62 ± 9 years and drug-refractory NYHA class III heart failure with optimised medical therapy (Table 1) were enrolled in the study. The underlying heart disease was idiopathic dilated cardiomyopathy in 11 patients, coronary heart disease in 13 patients, and dilated cardiomyopathy 9 years after cardiac transplantation in 1 patient.

On average, 1.9 ± 1.7 right ventricular lead positions were tested. Upon acute testing, the mean increase in dP/dt was $6.9 \pm 2.7\%$. In all patients testing included CCM stimulation with a maximum output of 7.73 V. In 23 patients (92%) the CCM system was implanted successfully. In two patients the device could not be implanted because of intolerable symptoms from phrenic nerve stimulation (patient #18) and failure to achieve a sufficient increase in dP/dt (patient #25), respectively. In one patient with ischaemic cardiomyopathy, who was identified as at high risk for sudden cardiac death by programmed stimulation, a cardioverter-defibrillator (Medtronic 7231, Kerkrade, The Netherlands) was im-

Table 1 Concomitant medical therapy of the population

ACE inhibitor	25 patients	100%
β-Blocker	22 patients	88%
Spironolactone	13 patients	52%
Furosemide	22 patients	88%
Digoxin	12 patients	48%

planted at the same time. This patient developed pocket haematoma of both the CCM generator and implantable defibrillator postoperatively, requiring surgical revision. In all other patients the postoperative course was uneventful.

Overall, the clinical condition of the patients improved significantly (Fig. 4). Left ventricular ejection fraction and quality of life significantly improved from $22 \pm 7\%$ to $28 \pm 8\%$ ($p = 0.0002$) and from 43 ± 22 to 25 ± 18 ($p = 0.001$), respectively (Table 2). The 6-min walk test, performed in 7 patients at one of the participating centres, increased from 411 ± 86 to 465 ± 81 m ($p = 0.02$).

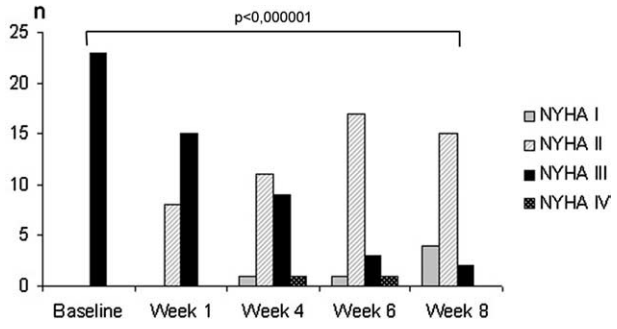

Fig. 4 Clinical condition of the patients in the course of the study.

In the patient with heart transplantation, atrial undersensing with automatic device inhibition and immediate clinical deterioration occurred three weeks after device implantation. After successful reprogramming of the device, the patient recovered and his left ventricular ejection fraction improved from 35% at baseline to 46% after 8 weeks of follow-up. Two sudden deaths occurred during follow-up (patients #11 and #23). Both were witnessed and occurred off CCM stimulation. The lethal arrhythmias were ventricular fibrillation and asystole, respectively. Eight patients (35%) intermittently reported mild sensations associated with CCM signal application. In one patient (4%) sensations were intolerable, requiring lead repositioning. Holter recordings during follow-up demonstrated no significant differences in the frequency or severity of ventricular arrhythmias compared to baseline.

Discussion

This is the first human study with implanted devices demonstrating that nonexcitatory stimulation during the absolute refractory period significantly improves both systolic function and clinical parameters in patients with drug-refractory chronic heart failure.

In good accordance with experimental studies[3,7] and studies in humans in the electrophysiologic laboratory,[8]

Table 2 Clinical results of 23 patients with an implanted CCM generator

Patient #	LV-EF (%)		MLwHFS		6-min Walk test (m)	
	Baseline	Week 8	Baseline	Week 8	Baseline	Week 8
1	13	25	45	42		
2	21	20	33	12		
3	24	40	8	20		
4	24	25	30	33		
5	24	35	17	11		
6	30	28	58	35		
7	22	25	40	18		
8	12	14	83	1		
9	30	28	62	54		
10	13	20	86	67		
11	25		73			
12	14	25	20	5	370	392
13	31	34	49	10	480	534
14	35	46	67	45		
15	17	23	50	20		
16	18	37	38	3	390	450
17	30	35	20	23	375	435
19	28	37	12	7	315	396
20	13	23	21	26	570	615
21	26	25	29	21	375	430
22	21	19	46	46		
23	16		39			
24	18	30	63	18		
Mean	22	28	43	25	411	465
SD	7	8	22	18	86	81
p	$p = 0.0002$		$p = 0.001$		$p = 0.02$	

CCM, cardiac-contractility modulation; LV-EF, left ventricular ejection fraction; MLwHFS, Minnesota Living with Heart Failure Score.

intraoperative testing showed an immediate increase in d*P*/d*t* upon CCM initiation, which was maintained during signal delivery. As stipulated by the protocol to allow device implantation, a minimum increase in d*P*/d*t* of 5% was seen in almost all patients (96%) irrespective of the underlying heart disease. This response of d*P*/d*t* during acute testing was transformed into a sustained increase in left ventricular ejection fraction that was paralleled by an improvement in clinical parameters during follow-up. A placebo effect due to device implantation appears unlikely since device therapy was only allowed in patients that showed substantial haemodynamic improvement during acute intraoperative testing. Nevertheless, in order to evaluate the contribution of a device-placebo effect to the clinical effects observed during a more extensive follow-up, a prospective double blind study is required.

Although CCM stimulation was carried out only 3 h a day, the increase in systolic function was sustained for at least several hours upon CCM termination, since a significant increase in the ejection fraction was demonstrated when the device had been inactive for at least 12 h. How long the beneficial effect of intermittent CCM stimulation is sustained cannot be answered by our data. However, as seen in one of the patients, whose device was inhibited by atrial undersensing, the inotropic effect may gradually disappear, resulting in concomitant clinical deterioration.

The precise mechanism by which CCM stimulation exerts its beneficial effects remains unknown. In particular, the phenomenon whereby right ventricular septal stimulation results in significant improvement of left ventricular systolic function cannot be fully explained at this point in time and requires further investigation. One of the hypotheses of nonexcitatory stimulation postulates that the high-energy electrical current applied during the absolute myocardial refractory period results in prolongation of the duration of the action potential with a concurrent increase in calcium delivery to myofilaments.[2,3]

The high current necessary for sufficient prolongation of the action potential may cause intermittent sensations: in 1/25 patients, phrenic nerve stimulation precluded device implantation and in 8/23 chronically implanted patients, intermittent mild sensations associated with CCM stimulation occurred during follow-up. This phenomenon occurred although intraoperative high-output testing had been negative in these patients, even necessitating surgical lead repositioning in one patient. This may best be explained as a posture-related phenomenon. Intraoperatively, acute testing is performed in the supine position whereas in the clinical setting CCM stimulation occurred mainly in the standing or sitting position, which changed the anatomic distance between the phrenic nerve and site of stimulation.

Apart from these minor sensations, which did not have a significant impact on quality of life in the vast majority of the patients, no device-related complications were observed. In particular, no proarrhythmic effects associated with this therapy were observed during Holter monitoring.

However, two patients with ischaemic cardiomyopathy died suddenly during follow-up. Both deaths were witnessed and occurred at a time when the implanted devices were inactive. Thus, a causal relationship between CCM and the sudden deaths appears unlikely. Patients with ischaemic cardiomyopathy are at high risk for sudden cardiac death[9] and concomitant implantable cardioverter-defibrillator use is highly recommended. However, in patients with nonischaemic cardiomyopathy the role of prophylactic ICD therapy has not yet been defined. As to whether the positive inotropic effect of CCM therapy may increase the risk of sudden cardiac death in patients with severely depressed left ventricular function needs further investigation.

The application of CCM stimulation for 3 h a day was chosen arbitrarily in this study because no experience of chronic CCM application in humans was available prior to this study. The energy requirements of biphasic impulses of 7.7 V/5.4 ms are high, which will result in an expected longevity of CCM devices of approximately one year with current battery systems. Therefore, dose-finding studies, including application of CCM on demand upon clinical grounds and/or different stimulation modes, are mandatory.

Conclusion

Although CCM is still highly experimental and the underlying cellular mechanisms are not fully understood, nonexcitatory cardiac stimulation seems to be a promising technique to significantly improve both clinical condition and systolic ventricular function in patients with drug-refractory chronic heart failure. Further studies are required to precisely define the underlying mechanism and determine the most effective mode of application.

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