



Cardiac contractility modulation: first experience in heart failure patients with reduced ejection fraction and permanent atrial fibrillation

Susanne Röger*, Raphaela Schneider, Boris Rudic, Volker Liebe, Ksenija Stach, Rainer Schimpf, Martin Borggrefe, and Jürgen Kuschyk

I. Medical Department, University Hospital Mannheim, Theodor-Kutzer-Ufer 1-3, Mannheim D-68167, Germany

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Aims

Cardiac contractility modulation (CCM) is an electrical therapy for heart failure (HF) with reduced ejection fraction. Sinus rhythm is deemed necessary for effective treatment because the current CCM signal delivery algorithm requires sequential sensing of a p wave, followed by depolarizations at each ventricular lead. In case of atrial fibrillation (AF) CCM is inhibited. This study demonstrates the feasibility of CCM therapy in patients with permanent AF by circumventing the requirement for sensing of a natural p wave.

Methods and results

Five CCM patients with AF received a pacemaker or implantable cardioverter/defibrillator (ICD) upgrade to cardiac resynchronization therapy (CRT) with low atrial sensitivity, which resulted in compulsory atrial stimulation followed by biventricular pacing. The CCM system recognized the atrial stimuli as p waves, which led to CCM signal delivery. Three patients developed permanent AF after a mean follow-up of 40 months of CCM therapy. Two patients had permanent AF at the time of CCM device implantation. All pacemaker or ICD devices were successfully upgraded to CRT. Cardiac resynchronization therapy stimulation rates of $\geq 96\%$ and CCM stimulation rates between 60% and 95% were achieved. Clinical condition of the patients improved (mean NYHA class -0.7 , left ventricular ejection fraction $+2\%$, Minnesota living with HF questionnaire -15.6 points).

Conclusion

CCM signal delivery is feasible in HF patients with permanent AF by sequential atrial-ventricular pacing, so that the atrial pacing spike is interpreted as a p wave by the CCM signal delivery algorithm. This experimental approach can be considered in individual cases. A new CCM algorithm, which does not require an atrial electrode, is desirable.

Keywords

Cardiac contractility modulation • Heart failure • Cardiac resynchronization therapy • Atrial fibrillation

Introduction

Despite advances in therapeutic targets and interventions, heart failure (HF) remains a critical problem and heavy burden to the health care systems in developed countries.^{1,2} Cardiac resynchronization therapy (CRT) reduces hospitalizations and mortality in patients with HF with reduced ejection fraction and wide QRS duration.^{3–6} However, according to the guideline-recommended selection criteria, only a portion of HF patients are suitable candidates for CRT and approximately one-third of patients receiving a CRT device are nonresponders.^{2,7} There is thus a need to identify alternative device-based treatments for patients with persistent symptoms despite optimal medical therapy (OMT), especially for those with normal QRS duration.⁸

One cellular defect that underlies myocardial contractile dysfunction in HF is alteration of the intracellular calcium homeostasis in the cardiomyocytes.⁹ Cardiac contractility modulation (CCM) is an established electrical device-based approach proposed for enhancing ventricular contractile strength of the failing myocardium independent of the synchrony of myocardial contraction. Cardiac contractility modulation signals are non-excitatory electrical impulses of relatively high voltage that are applied during the absolute refractory period. These signals do not initiate a new contraction but modify calcium homeostasis in the cardiomyocyte and enhance its contractility without increasing the myocardial oxygen consumption. Cardiac contractility modulation has been investigated in several experimental, preclinical, and clinical studies that evaluated the safety and

* Corresponding author. Tel: +49 621 383 4231; fax: +49 621 383 3061. E-mail address: susanroeger@hotmail.com

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What's new?

- It was demonstrated for the first time, that CCM therapy is feasible in HF patients with permanent AF through the use of CRT to circumvent the limitation of the current CCM signal delivery algorithm, by providing a p wave surrogate, and to ensure consistent rhythmic ventricular excitations.
- This experimental approach can be considered in individual cases.

effectiveness of the therapy and explored the underlying molecular mechanism associated with the therapy.^{10–16}

Two prospective randomized multicenter studies have demonstrated improvements in NYHA functional classification, quality of life indexed by Minnesota living with heart failure questionnaire (MLWHFQ) and peak oxygen uptake (peak VO₂) during cardiopulmonary exercise testing.^{17,18} Furthermore, CCM may contribute to left ventricular reverse remodelling and improve systolic ventricular function.¹⁹ In a retrospective study, Schau *et al.* could demonstrate that CCM therapy is safe, as it has no adverse effect on long-term survival.²⁰ A small case series demonstrated that the combination of CCM therapy in addition to CRT is feasible and that CCM can be a possible useful adjunct in CRT non-responder patients.²¹

With the current device, called the Optimizer™ (Impulse Dynamics), sinus rhythm (SR) is considered mandatory for CCM treatment because the current CCM signal delivery algorithm requires sequential intra-cardiac sensing of a p wave, followed by appropriately timed ventricular activations by the two ventricular septal leads. The current CCM device contains a built-in algorithm that inhibits delivery of a CCM signal when an irregular electrical activity is detected, such as premature atrial or ventricular complexes or sensing defects. This is designed to eliminate the possibility of CCM signal delivery during a T wave, which has the potential to induce an arrhythmia.

In case of atrial fibrillation (AF), CCM therapy is inhibited due to loss of the p wave. For this reason, the therapy is currently being provided to patients with SR and to patients with intermittent AF, who receive the therapy during periods of SR. The therapy is currently not being provided to patients with permanent AF, as the therapy would be continuously inhibited in those cases. However, AF is one of the most frequent comorbidities in patients with HF and in advanced HF it occurs in up to 50% of the patients,^{22,23} many of them have permanent AF and therefore are currently ineligible for CCM therapy.

The purpose of this study was to demonstrate, for the first time, the feasibility of CCM therapy in HF patients with permanent AF by circumventing the limitation of the current CCM signal delivery algorithm while, at the same time, retaining its safety features.

Methods

Between December 2002 and May 2013, 87 consecutive patients with HF with reduced ejection fraction received an Optimizer™ device (Impulse Dynamics) at our referral center for CCM therapy. Ten of these patients received the device between December 2002 and August 2005 within the context of the FIX-CHF-4, European study.¹⁷ Seventy-seven of the patients received the device after the Optimizer™ received the

European community mark. The key inclusion and exclusion criteria were similar to those in the various CCM studies.^{17,18,24} Specifically, patients were required to be on appropriate, stable medical treatment for HF, including (unless shown to be intolerant) a beta-blocker, an angiotensin-converting inhibitor or angiotensin II receptor blocker, and a mineralocorticoid receptor antagonist. Unless there were extenuating circumstances, subjects were required to have an implantable cardioverter/defibrillator (ICD).

Cardiac contractility modulation therapy was not offered to patients who were dependent on inotropic medications, who had a high number of premature ventricular contractions (>8900 per 24 h on a baseline Holter ECG), who had a myocardial infarction within 90 days, or who had percutaneous coronary intervention within 30 days or coronary artery bypass surgery within 90 days.

The patients underwent baseline evaluation, which included a 24 hours Holter monitor, determination of NYHA functional class stadium, MLWHFQ and baseline echocardiography. Echocardiographic data including left ventricular ejection fraction (LVEF) were acquired with Vivid 7 and Vivid i (GE healthcare) ultrasound scanners. Cardio-pulmonary exercise testing was performed in patients who were able to cycle.

The implant procedure and electrical characteristics of CCM signals have been detailed previously.^{17,24} Briefly, the Optimizer™ system consists of an implanted pulse generator and three pacing leads (a standard right atrial lead and two active fixation leads placed at the septum of the right ventricle). Between 2005 and January 2013 patients received the Optimizer™ III system,²⁴ which contains a rechargeable battery. The Optimizer™ IVs system became available in February 2013, which is significantly smaller than its predecessor. Active CCM treatment was delivered for a minimum of seven 1 hour periods spaced equally over the day. Depending on clinical therapeutic success CCM treatment duration could be extended to maximum 12 hours daily.

At the time of CCM device implantation nine of the 87 consecutive patients were known to have paroxysmal AF, nine patients had a history of successful cardioversion after persistent AF, and 67 of the 87 patients had no history of AF.

Three of the 87 consecutive patients developed permanent AF after a mean follow-up time of 40 months and therefore their CCM therapy was subsequently inhibited. Two patients had permanent AF at the time of CCM device implantation. They asked about the therapy because of a lack of alternative therapeutic methods. Both patients were informed of the off-label use of the Optimizer™ device in this manner and gave informed consent.

Existing ICDs or pacemakers were upgraded to CRT devices with atrial sensitivity programmed to 4 mV (intentionally low, to achieve atrial under-sensing) and achieve compulsory atrial stimulation by the CRT device. Atrial signals were followed by biventricular pacing signals. The CCM system recognized the atrial stimuli as p waves, which in combination with the reliably paced ventricular beats, led to successful CCM therapy delivery. The study complies with the Declaration of Helsinki, the research protocol is approved by the locally appointed ethics committee, the informed consent of the subjects has been obtained.

Results

Three of the 87 consecutive patients (Table 1, patients 1–3) developed permanent AF after a mean follow-up of 40 months with CCM therapy. At the time of CCM implantation, patients 1 and 2 had shown no signs of AF. Patient 3 had paroxysmal AF. Historically, 6 months after beginning CCM therapy these three patients showed clinical improvements (mean change of +2% in LVEF, –0.67 in

Table 1 Demographic baseline data of the five patients with permanent atrial fibrillation before the combined activation of CRT and CCM

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	64	61	79	74	68
Gender	F	M	M	M	F
BMI (kg/m ²)	34	32	23	26	37
Date of CCM implantation	3/2004	12/2011	5/2011	1/2012	4/2012
Date of CRT upgrade	4/2012	10/2012	6/2013	1/2012	3/2012
Aetiology of CMP	Ischaemic	Ischaemic	Ischaemic	Ischaemic	Nonischaemic
Prior MI	Yes	Yes	Yes	Yes	No
Prior CABG	Yes	Yes	Yes	No	No
Diabetes	No	No	No	Yes	Yes
Renal insufficiency	Yes	No	No	Yes	No
Baseline medication					
ACE inhibitor	Yes	Yes	Yes	Yes	Yes
Beta-blocker	Yes	Yes	Yes	Yes	Yes
Mineralocorticoid receptor antagonist	Yes	Yes	Yes	No	Yes
Digitalis	No	No	No	Yes	Yes
Diuretic	Yes	Yes	Yes	Yes	Yes
QRS width in ms	110	110	120	175 (stimulated)	100

CRT, cardiac resynchronization therapy; CCM, cardiac contractility modulation; F, female; M, male; BMI, body mass index; CMP, cardiomyopathy; MI, myocardial infarction; CABG, coronary artery bypass graft.

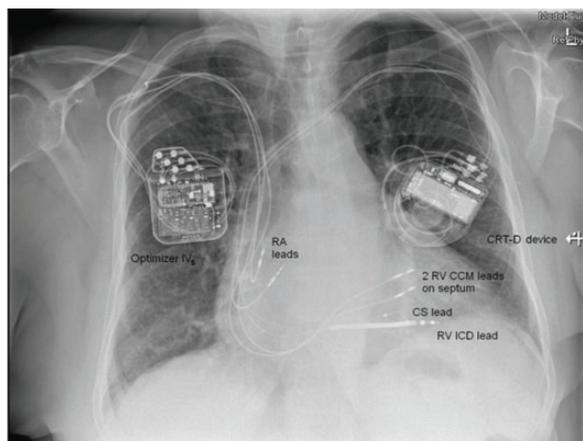


Figure 1 Chest x-ray of patient 5 with CRT-D device at the left and CCM device at the right side of the thorax. RA, right atrial; RV, right ventricular; CS, coronary sinus.

NYHA class, -12.3 points in MLWHFQ, and +1.7 mL/kg/min in peak VO₂). In all three cases, AF caused inhibition of CCM therapy.

Two of the 87 consecutive patients (Table 1, patients 4 and 5) had permanent AF at time of implantation of the CCM device. These two patients were in NYHA class IV with recurrent hospitalizations for cardiac decompensation with pleural effusion and edema despite OMT. No other therapeutic options were available for them. Patient 4 received an upgrade to a CRT pacemaker (CRT-P) simultaneously with the implantation of the CCM device in January 2012.

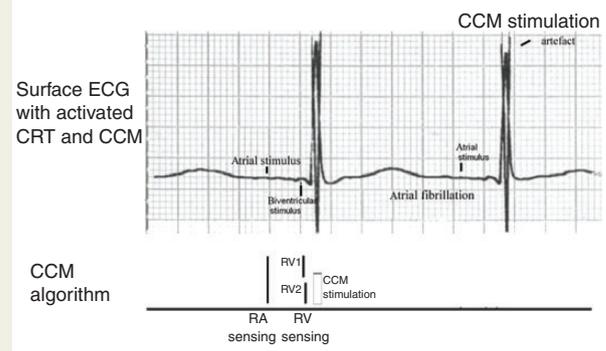


Figure 2 Surface ECG of patient 2 with AF, intentional atrial stimulation and biventricular stimulation, CCM stimulation artefacts occur during the QRS complexes at proper timing. The corresponding CCM algorithm is shown at the bottom of the figure.

Patient 5 received a CCM device in April 2013 four weeks after upgrading the ICD to a CRT defibrillator (CRT-D) device.

In all five patients the system upgrades to CRT were performed without complications. Figure 1 shows the chest x-ray of patient 5. Patients 1, 2, 3, and 5 received a CRT-D due to markedly reduced LVEF. Patient 4 received a CRT-P device because his LVEF was only moderately reduced. The demographic baseline data before the combined activation of CCM and CRT of all five patients are demonstrated in Table 1.

In all five patients, intentional atrial under-sensing of the CRT was achieved by programming atrial sensitivity to 4 mV. This resulted in

Table 2 Technical data

Patient	CCM device	CRT device	Percentage of biventricular stimulation	Percentage of CCM stimulation (therapy time per day)
1	Optimizer™ III	CRT-D Medtronic Protecta	96%	60 (CCM 12 h)
2	Optimizer™ III	CRT-D Medtronic Protecta	98.5%	60 (CCM 12 h)
3	Optimizer™ III	CRT-D Medtronic Protecta	100%	70 (CCM 12 h)
4	Optimizer™ III	CRT-P Medtronic Consulta	100%	70 (CCM 12 h)
5	Optimizer™ IVs	CRT-D Medtronic Protecta	100%	95 (CCM 10 h)

CCM, cardiac contractility modulation; CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker.

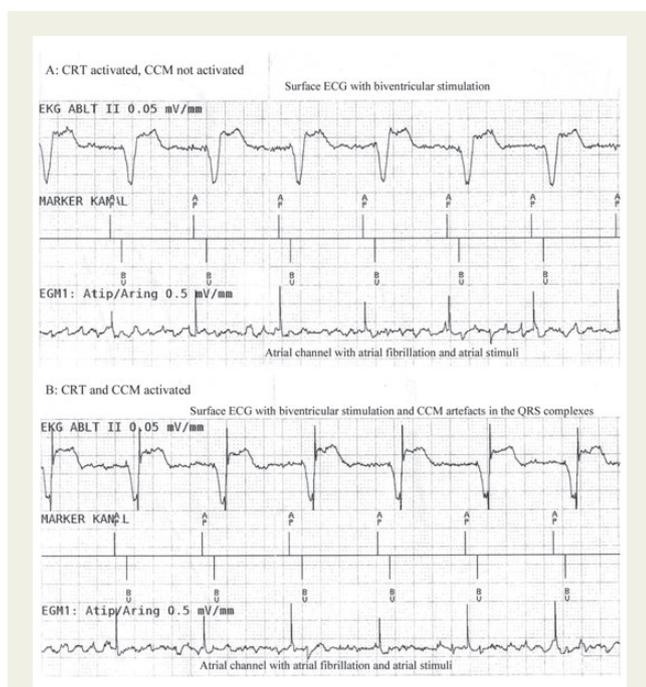


Figure 3 Cardiac resynchronization therapy defibrillator inter-rogation of patient 5: the CRT is activated, the marker channel shows atrial pacing and biventricular pacing, the atrial channel shows AF with intentional atrial stimulation. (A) Inactivated CCM. (B) Activated CCM with CCM stimulation artefacts occurring during the QRS complexes at proper timing.

100% atrial stimulation by the CRT device in all patients as shown in Figure 2. In patients 1, 2, and 4, biventricular stimulation rates of >96% were reached immediately. In patients 3 and 5 intrinsic ventricular conduction caused intermittent inhibition of the biventricular stimulation in DDD mode. Therefore, these two patients underwent atrio-ventricular nodal ablation. After this, they had biventricular stimulation rates of 100%. Cardiac contractility modulation stimulation rates between 60% and 95% were achieved (Table 2 and Figure 3).

As of October 2013, all five patients are alive. The clinical condition of each patient has improved. Table 3 compares the findings for LVEF, NYHA class, MLWHQ, and peak VO_2 before the combined activation of CRT and CCM with the current clinical data (obtained within the last four months). The average follow-up period since the CRT-CCM combined activation is ~13 months. Mean LVEF increased by 2%, mean NYHA class decreased by 0.7, and mean MLWHQ decreased by 15.6 points. Cardio-pulmonary exercise testing was performed in two of the patients, as the other patients were not able to cycle because of orthopedic reasons (arthrosis of knee or hip). Mean increase of peak VO_2 in the two patients was 1.65 mL/kg/min.

Before implantation of the CCM device four patients had mild tricuspid regurgitation, one patient had moderate tricuspid regurgitation. Despite every patient receiving three right ventricular electrodes (one of the ICD, two of the CCM), only one patient developed moderate tricuspid regurgitation. No case of severe tricuspid regurgitation occurred.

Discussion

Cardiac contractility modulation is an innovative therapy for HF patients with reduced ejection fraction.^{17,18,24,25} Sinus rhythm has previously been considered a requirement for CCM therapy with the current Optimizer™ device, because stimulation is inhibited in case of AF by its signal delivery algorithm. However, up to 50% of patients with advanced HF suffer from AF, which contributes significantly to worsening of symptoms and prognosis. As a result, CCM therapy, like CRT therapy, is currently restricted to a limited number of HF patients. Nagele *et al.* demonstrated that the combination of both techniques can be performed safely and that CCM can be a possible useful adjunct in CRT non-responder patients.²¹

It has been demonstrated for the first time in the present study that CCM therapy is feasible in HF patients with permanent AF, and that the use of CRT can be implemented to circumvent the limitation of the current CCM signal delivery algorithm, by providing a p-wave surrogate and ensuring consistent rhythmic ventricular excitations, as required by the CCM signal delivery algorithm.

Table 3 Left ventricular ejection fraction, NYHA Class, MLWHFQ and CPX before combined activation of CRT + CCM and at last follow-up

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
LVEF before CRT + CCM activation	25%	15%	20%	42%	28%
LVEF at last follow-up	30%	15%	20%	45%	30%
NYHA Class before CRT + CCM activation	II-III	III-IV	III	IV	IV
NYHA Class at last follow-up	II	III	II-III	III	III
MLWHFQ before CRT + CCM activation	35	69	43	56	47
MLWHFQ at last follow-up	20	51	40	36	25
CPX peak VO ₂ (mL/kg/min) before CRT + CCM activation	20.4	11.1	Not possible	Not possible	Not possible
CPX peak VO ₂ (mL/kg/min) at last follow-up	21.8	13.0	Not possible	Not possible	Not possible

LVEF, left ventricular ejection fraction; MLWHFQ, Minnesota living with heart failure questionnaire; CPX, cardiopulmonary exercise testing; CRT, cardiac resynchronization therapy; CCM, cardiac contractility modulation; peak VO₂, peak oxygen uptake.

Five patients with HF with reduced ejection fraction and permanent AF who had no alternative therapy options were successfully treated by CCM. Although multiple electrodes had to be implanted, no case of severe tricuspid regurgitation occurred.

To date, permanent AF is a contraindication for initiation of CCM therapy. Precondition of effective biventricular stimulation of patients with AF in the DDD mode is constant intrinsic ventricular conduction of <60/min. Therefore, atrio-ventricular nodal ablation would be required in many cases.

This experimental approach can be considered in individual cases. A new CCM algorithm, which does not require an atrial electrode for sensing and triggering of CCM therapy, is desirable for widespread application of CCM therapy in HF patients having permanent AF.

Conflict of interest: Susanne Röger, Martin Borggrefe and Jürgen Kuschyk participate in clinical studies of Impulse Dynamics and Medtronic. All other authors have no conflict of interest to declare.

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