

Cardiac contractility modulation in non-responders to cardiac resynchronization therapy

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Aims Cardiac resynchronization therapy (CRT) has become a standard therapy in cases of heart failure and asynchrony. Unfortunately, 20–30% of patients were non-responsive (NR) to CRT. In this report we used cardiac contractility modulation (CCM) as an adjunctive measure in NR patients.

Methods and results Sixteen NR patients, mean age 65 ± 9 years, mean ejection fraction $27.3 \pm 7.4\%$, and New York Heart Association (NYHA) class III ($n = 9$) or IV ($n = 7$) despite CRT plus optimized medical therapy, received an additional CCM-implantation contra-lateral to the existing CRT system (OPTIMIZER III, Impulse Dynamics, Orangeburg, NY, USA). Cardiac contractility modulation delivers non-excitatory high-energy stimulatory impulses during the absolute refractory period, thus improving contractility [left ventricular (LV) dp/dt] by stimulating the septum with two screw-in leads and one additional atrial lead for triggering the impulses. Acute LV dp/dt changes induced by CCM stimulation were measured by 5F Millar catheters placed in the LV during the implantation procedure in 14 of 16 cases. Patients were followed prospectively. Left ventricular dp/dt increased from a mean of 568 ± 153 to 646 ± 147 mmHg/s (+14%, $P < 0.001$) in the acute intraoperative testing. We noted the following complications and events during a follow-up of an average of 147 ± 80 days (range 68–326) after CCM: intraoperative ventricular flutter needing cardioversion ($n = 1$), atrial lead dislocation ($n = 1$), coronary sinus (CS) lead dislocation ($n = 1$), painful stimulation requiring repositioning of septal leads ($n = 1$), true defibrillator shocks ($n = 3$), cardiac decompensations ($n = 3$), atrial fibrillation ($n = 4$), renal failure ($n = 1$), and pneumonia ($n = 2$). NYHA class improved from 3.4 to 2.8 ($P < 0.01$), and the ejection fraction increased from 27.3 ± 5 to 31.1 ± 6 ($P < 0.01$). Three patients (19%) died suddenly presumably due to electromechanical dissociation after 318, 104, and 81 days. No electrical interference was observed between the CCM and CRT systems, and in particular, at no time was the CRT-implantable cardioverter-defibrillator found to be delivering inadequate shocks.

Conclusion The CCM method is feasible and could be applied with calculated risks as a possible useful adjunct in CRT-NR when no other options are available; however, mortality and event rates are high in this very sick population.

Introduction

Cardiac resynchronization therapy (CRT) has become a standard therapy in cases of heart failure and inter- and intra-ventricular conduction disturbances.¹ Unfortunately, 20–30% of patients were non-responsive (NR) to CRT.² Adjunctive measures for these refractory patients are needed. In this regard, the technique of cardiac contractility modulation (CCM) has recently been introduced.^{3–6} It delivers non-excitatory high-energy stimulation impulses during the absolute refractory period, thus improving contractility (LV dp/dt) by hitherto not well-characterized mechanisms.

For example, CCM may modulate the amplitude and duration of membrane depolarization and may therefore influence calcium fluxes.⁷ Changes in myocardial gene expression (including a reversal of several aspects of the foetal gene program expressed in heart failure) and improved expression and phosphorylation of the sodium–calcium exchanger, phospholamban, and connexin are also described.^{8,9}

Cardiac contractility modulation works by stimulating the septum with two screw-in leads, and one additional atrial lead is used to trigger the impulses.⁹ Unlike deleterious positive inotropic drugs, the increase in LV function during CCM therapy is elicited without increasing myocardial oxygen consumption.^{9,10} Recently, a randomized study showed improved exercise capacity of patients under CCM stimulation compared with patients with CCM stimulation turned off.¹¹

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However, all of these above-mentioned trials excluded patients with existing resynchronization devices.

An initial single case report suggested a clinical benefit in a CRT-NR patient after additional CCM implantation.¹² Therefore, we sought to investigate the feasibility of this new therapy in a larger CRT-NR series.

Methods

The protocol was approved by the Bad Segeberg Ethics Committee and patients gave written informed consent. CRT-NR patients were defined as patients remaining in NYHA classes III–IV despite optimized biventricular pacing and a complete heart failure therapy consisting of at least β -blockers, angiotensin-converting enzyme inhibitors or AT1 antagonists, and diuretics for at least 3 months. Cardiac resynchronization therapy-non-responders were collected from our CRT and heart failure program (~120 CRT implantations per year). NYHA classification was defined as follows: Class III: patients with marked limitation of activity but comfortable at rest. Class IV: patients at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Sixteen CRT-NR patients with either sinus rhythm or stimulated atrium (mean age 65 ± 9 years, mean LVEF $27.3 \pm 7.4\%$ and NYHA class III ($n=9$) or IV ($n=7$)) were selected for additional CCM-implantation (OPTIMIZER III, Impulse Dynamics, Orangeburg, NY, USA). The implanted CRTD devices were as follows: Sentry (Medtronic, $n=2$), Insync 3 Marquis (Medtronic, $n=6$), Maximo (Medtronic, $n=1$), Kronos LVT (Biotronik, $n=4$), Ovatio CRT (Sorin, $n=1$), and Atlas 2 (ST Jude Medical, $n=2$).

The positioning of the coronary sinus (CS) leads was as follows: anterior ($n=3$), anterolateral ($n=4$), posterolateral ($n=8$), and posterior ($n=1$). The mean time of CRT therapy before CCM implantation was 1.9 ± 0.8 years (range 0.6–3.0). Heart transplantation was considered to be contraindicated or not possible in these patients for the following reasons: patient refusal ($n=1$), high pulmonary vascular resistance ($n=1$), alcoholism ($n=1$), severe diabetes with renal failure ($n=2$), or age >65 years ($n=11$). Cardiac resynchronization therapy pacing was performed as AV sequential biventricular pacing with AV and VV intervals optimized by standard echocardiography. A repositioning of the LV lead in patients with anterior positions was rejected due to a lack of suitable veins as visualized in CS angiograms during the first implantation procedure. Detailed characteristics of the NR patients are listed in Table 1.

Implant procedure

Ventricular tachycardia detection algorithms of the CRT-D devices were turned off during CCM implantation to prevent inadequate shocks provoked by coagulation, pace configurations were not changed. Acute LV dp/dt changes from baseline measurements during biventricular pacing induced only by CCM stimulation were measured using 5F Millar micromanometer catheters (Millar Instruments, Houston, TX, USA) placed in the LV during the implantation procedure through 6F introducer sheaths placed in the right femoral artery. A pocket was generally made in the right subclavian region and three electrodes were introduced into the subclavian vein after puncture or cephalic vein preparation by a standard procedure. One electrode was positioned in the right atrium and was used for sensing atrial activity. The other two electrodes were positioned on the right ventricular septum. These electrodes were advanced under fluoroscopic guidance. A minimal interlead distance of 2 cm was chosen. The response to acute CCM stimulation was measured through online assessment of changes in LV dP/dt (measured using Millar catheters). The baseline value was allowed to stabilize at least for 15 min prior to start of CCM stimulation. If the initial electrode placement did not result in the pre-specified increase in dP/dt of $\geq 5\%$, the electrodes were repositioned until

Table 1 Baseline characteristics of 16 CRT-NR patients who underwent additional CCM implantation

Age (years)	65 ± 9 (42–80)
Male	$n = 12$ (75%)
NYHA prior to CRT	3.4 ± 0.4
LVEF prior to CRT	24.1 ± 8.3
QRS width prior to CRT	175 ± 35
QRS width during CRT	153 ± 28
CRT delivery time prior to CCM (years)	1.9 ± 0.8
Mean hospitalizations 1 year prior to CCM per patient	2.63 ± 2
Mean in-hospital days 1 year prior to CCM per patient	30 ± 23
Dilated cardiomyopathy	$n = 6$
Ischaemic cardiomyopathy	$n = 10$
Anterior CS-lead position	$n = 3$
Anterolateral CS-lead position	$n = 4$
Posterior CS-lead position	$n = 1$
Posterolateral CS-lead position	$n = 8$
ACEI/AT1 antagonists (%)	100
β -Blockers (%)	100
Spironolacton (%)	75

this effect was achieved. After each repositioning, a new baseline measurement was done after an at least 15-min stabilization phase. The patient was under light sedation with midazolam and normally was unaware of the stimulation mode. In two patients with occlusive disease of the femoral arteries, CCM implantation was performed without pressure control. Therefore, haemodynamic measurements were available only in 14 cases.

Device programming

The OPTIMIZER III system parameters are set through a programmer that transcutaneously communicates with the implanted device. The OPTIMIZER system is designed to inhibit CCM pulse delivery in the case of arrhythmia. This is possible through atrial sensing, which inhibits CCM signal delivery during arrhythmias. The timing windows for each electrode are programmed for each patient individually (the refractory period). After the operation, a cross-talk test was performed to exclude far-field- or oversensing of the defibrillator, which may cause inadequate sensing of ventricular tachycardia or ventricular fibrillation. Atrial and ventricular far field sensing of the CCM and CRT-D devices were eliminated by adapting the sensitivity threshold and by increasing of the refractory periods. Therapy periods alternated every other hour (i.e. a total of 12 h/day).

Follow-up

Patients were followed at regular intervals in our outpatient heart failure clinic. Patients and relatives were trained in the charging procedure. Normally, the CCM generator has to be charged every week. During the charging process, a warning signal is implemented that instructs the patient to inform his or her physician if the treatment was insufficient (treatment delivery $<40\%$). In this event, patients were instructed to come to the heart failure outpatient clinic for a system check. Routine CRTD and CCM system checks were performed at Days 1, 30, and 90, and every 3 months thereafter. Additional testing was performed in cases of clinical changes or in the event of the above-mentioned signal.

During routine checks, the percentage of therapy delivery was calculated. Cardiac contractility modulation devices were either reprogrammed in regard to sensing and timing and in two cases an antiarrhythmic drug (amiodarone) was given to reduce ventricular ectopic beats, which limits the therapy delivery.

Life quality was measured with a 21-item scale according to the 'Minnesota Living With Heart Failure Questionnaire' (MLHFQ).¹³

Blood levels of brain natriuretic peptide (BNP) were measured using the TRIAGE BNP test (Biosite Inc., San Diego, CA, USA). Echocardiography was performed with standard projections on a VIVID seven dimension machine (GE Healthcare, Chalfont, St. Giles, UK). Ejection fraction was measured with the biplane Simpson's method. It was not possible to make blind echo measurements due to the large visible device and stimulation spikes on the ECG monitor. Information on cardiac events were collected prospectively and continuously during the whole time period, whereas echo and BNP measurements were made only after 3 months.

Statistics

Differences in the results of clinical and haemodynamic data were checked for significance by means of Student's *t*-test for matched pairs. Non-parametric data were checked for significance with WILCOXON tests (Winstat 3.1, Kalmia Inc. and SPSS for Windows 6.1). All data are expressed as mean \pm standard deviation.

Results

The mean operation time was 113 ± 48 min and the mean fluoroscopy time was 8.4 ± 4.1 min.

Complications

Direct perioperative complications consisted of ventricular flutter two times during the placement of each septal lead

in one single patient. This patient had to be defibrillated twice. One postoperative apical pneumothorax was managed conservatively without drainage. In one patient, a dislocation of the CS lead occurred during placement of the CCM stimulator in the pocket. This patient had the CS lead implanted from the contralateral site due to a pipe-like CS main ostium. This patient needed a second CS lead implantation from the other site the following postoperative day. See *Figure 1* for an X-ray image of the final lead positions in the patient (seven leads). One patient with atrial lead dislodgement required the lead to be repositioned. A third patient developed painful chest stimulation. Obviously, his leads were anteriorly in the RV and stimulated the intercostal muscle. His CCM leads were repositioned from anterior septal to mid-apico septal.

Haemodynamic results

Left ventricular dp/dt measured in 14 patients out of 16 patients increased from 568 ± 153 to 646 ± 147 mmHg/s (+14%, $P < 0.001$) in the acute intraoperative testing. *Figure 2* shows an example of LV dp/dt increase in a CRT-NR patient showing marked fluctuations in contractility, which were obviously correlated with central apnea episodes in this particular case. In 8 out of 16 cases, intraoperative repositioning was necessary to yield a positive response. In six cases the second configuration and in two cases the third configuration were successful.

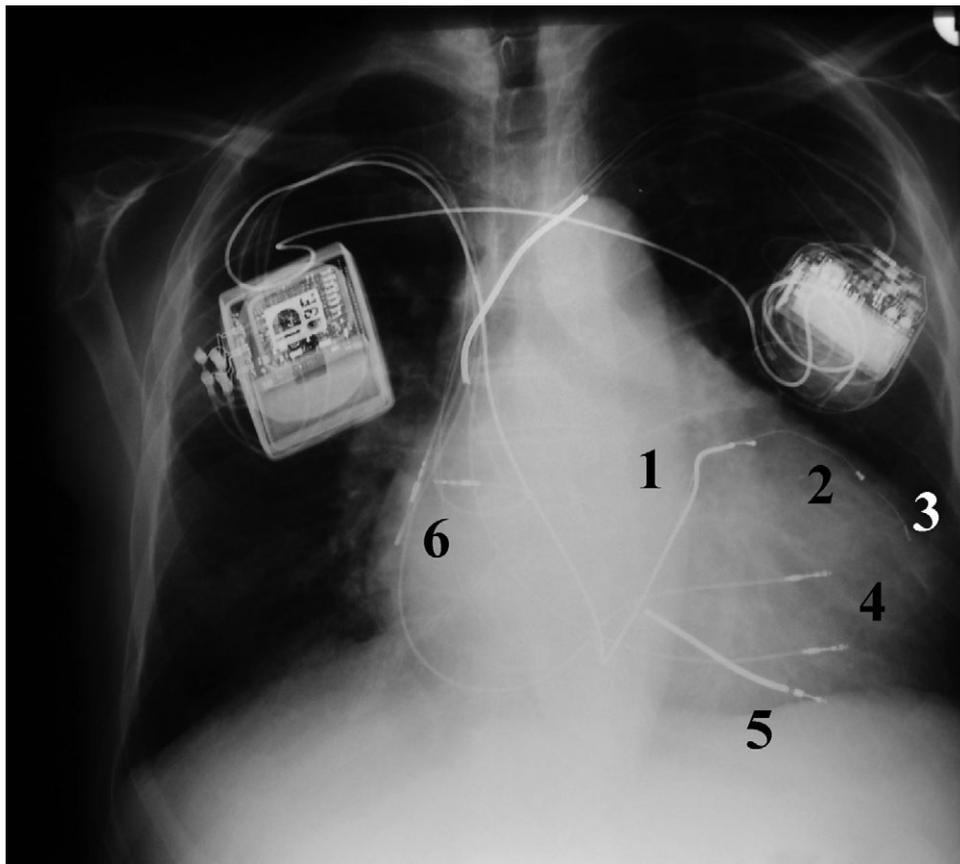


Figure 1 Final lead position in a CRT-NR patient. In this case, lead dislocation of the old CS lead¹ occurred during CCM generator placement. A second CS lead² had to be inserted on the second postoperative day. Fixation was only possible by leaving a retained guide wire in place.³ The other leads on this X-ray are the two septal CCM leads,⁴ the RV defibrillator lead,⁵ and the two atrial leads.⁶

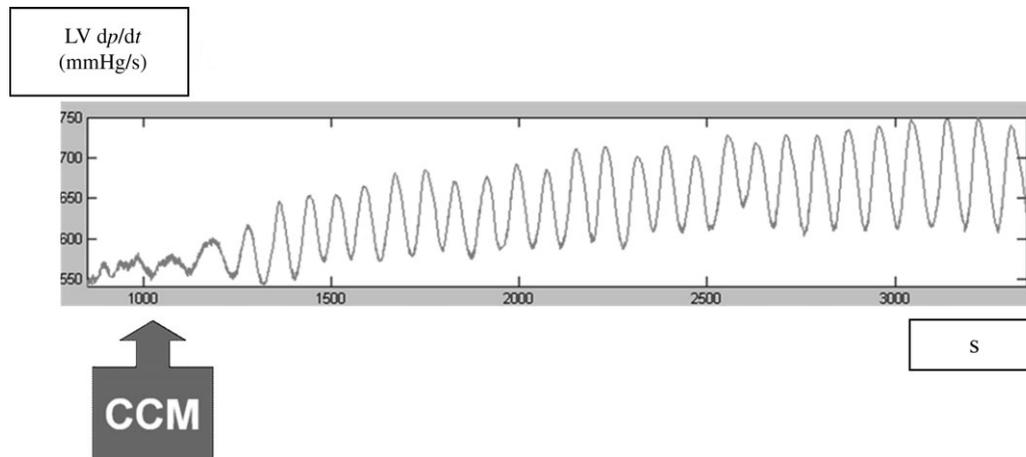


Figure 2 Left ventricular dp/dt increase (+23%) in a CRT-NR patient (NYHA IV) showing marked fluctuations in contractility patterns that were obviously correlated with central apnea episodes. LV dp/dt was measured using a Millar catheter placed in the LV using the right femoral artery.

Follow-up results

All patients could be discharged after the intervention. NYHA class improved from 3.4 to 2.8 ($P < 0.01$) and the ejection fraction increased from 27.3 ± 5 to 31.1 ± 6 ($P < 0.01$) at 3 months. On the basis of NYHA criteria, 10 patients (62%) were responders and 6 patients were non-responders to CCM. No relevant electrical interference was observed between the CCM and CRT systems and, in particular, at no time was the CRT-implantable cardioverter-defibrillator (CRT-ICD) found to be delivering inadequate shocks. Some patients had clinically irrelevant atrial far field sensing of the CCM stimulus. The following cardiac events were noted during a mean follow-up of 147 ± 80 days (range 68–326): true defibrillator shocks ($n = 3$), cardiac decompensations requiring hospitalization ($n = 3$), atrial fibrillation (AF) requiring cardioversion ($n = 3$), and pneumonia requiring hospitalization ($n = 3$). Three patients remained in NYHA classes III and IV and died suddenly due to documented electromechanical dissociation after 81, 104, and 318 days. Two of these patients had intermittent episodes of AF prior to death-preventing continuous CCM delivery. The first patient (#6) showed mode switch and AF in the 24 h prior to out-hospital death as revealed by his home-monitoring data transmission. The second patient (#9) was cardioverted three times due to documented AF in the days prior in hospital death. Cardiac contractility modulation delivery therefore was nearly zero during the period before his terminal event. In the third patient (#1), four episodes of ventricular fibrillation were detected and terminated correctly shortly before death. This patient showed a 100% CCM delivery in the days before. No tachycardiac final arrhythmia was stored in the CRT-D memory of the other three deceased patients. Two events were witnessed and external ECG monitoring showed clearly electro-mechanical dissociation (EMD). In one patient, post-mortem analysis was performed but no acute reason of death was found besides a critical heart weight of 1100 g.

A complete overview of operative and follow-up data for each patient is given in *Table 2*.

Discussion

In end stage heart failure, non-responders of CRT have a bad prognosis.¹⁴ Adjunctive measures are needed, and indeed

several options have to be considered, including: intravenous delivery of positive inotropic drugs,¹⁵ assist device implantation,¹⁶ stem cell infusion,¹⁷ alternative cardiac surgery techniques,¹⁸ or heart transplantation.¹⁹ However, all of these methods are either limited due to unproven efficacy (inotropic drugs, stem cells, and alternative surgical techniques) or due to a high complication rate combined with high costs and limited resources (assist devices, heart transplantation).

Our acute and short-term follow-up data are in line with earlier investigations, which reported that CCM stimulation gave additive acute effects to resynchronization in patients with mechanical asynchrony,²⁰ and that CCM improves exercise tolerance and life quality.¹¹ This may be because CRT and CCM exert their benefits through separate independent mechanisms.²¹

In our experience, CCM is technically feasible and may be a useful adjunct for CRT-NR and could be applied when no other options are available (*Table 2*). All of our CRT-NR patients responded acutely with an at least 5% increase in LV dp/dt (mean increase 14%—see Results and an example shown in *Figure 2*). However, in 2 out of 16 patients, this information was not available because Millar catheter placement was omitted due to significant peripheral vascular disease. This acute reaction may be due to an induction of gene expression within minutes following the application of electrical impulses.²² This fits to the impression of *Figure 2* that the maximal CCM effect needs some time for its full development.

Because all our 14 patients with measurements are acute responders, it might be feasible to implant CCM devices without acute haemodynamic measurements. However, in 8 of our 16 patients, an optimal response was possible only after intraoperative septal lead repositioning. Therefore, we recommend intraoperative testing at least until alternative parameters of treatment success become available. However, extensive intraoperative testing in some patients was the reason for the big variance in operation time.

As a result of the acute intervention, there were several early complications (*Table 2*), but all were managed without late sequelae. These included typical surgical complications as well as pneumothorax and atrial lead dislocation. It is interesting that we did not observe ventricular septal lead dislocation, but we did observe one case of ventricular flutter induced by manipulation at the

Table 2 Acute and follow-up complications in 16 CRT-NR patients after receiving additional CCM systems

Patient no.	Time of observation (days)	Time to complication (days)	Type of complication	Consequence measures	Outcome
1	318	220	Decompensation	Diuretics	Resolved
		318	True ICD shocks	None	Resolved
		318	EMD	CPR	Death
2	326	110	True ICD shock	Amiodarone	Resolved
3	249	-	None	None	-
4	167	-	None	None	-
5	167	-	None	None	-
6	104	36	Pneumonia	Antibiotics	Resolved
		103	Atrial fibrillation	None	Unresolved
		104	EMD	CPR	Death
7	146	53	True ICD shock	Amiodarone	Resolved
8	137	1	Pneumothorax	Wait and See	Resolved
		85	Decompensation	Diuretics	Resolved
9	81	1	Atrial lead dislocation	Repositioning	Resolved
		45	Decompensation	Diuretics	Resolved
		70, 75, 78	Atrial fibrillation	Cardioversion	Resolved
		70	Renal failure	Haemofiltration	Ongoing
10	130	81	EMD	CPR	Death
		48	Atrial fibrillation	Cardioversion	Resolved
11	119	1	Painful stimulation	Repositioning	Resolved
12	111	100	Pneumonia	Antibiotics	Resolved
13	90	37	Pneumonia	Antibiotics	Resolved
		42	Atrial fibrillation	Amiodarone	Resolved
14	69	-	None	None	-
15	69	-	None	None	-
16	68	-	None	None	-

EMD, electromechanical dissociation; CPR, cardiopulmonary resuscitation.

interventricular septum. Therefore, acute defibrillation capabilities (applied pads) should be routinely available during CCM implantation. Our one case with CS lead dislocation was curious, because the problem occurred only after insertion of the CCM stimulator in the generator pocket (*Figure 1*). The one patient with painful stimulation of the chest wall is also of interest. These sensations could not be managed by reprogramming the device to use a lower voltage. The lateral X-ray revealed that the septal leads were close to the anterior chest wall. Intercostal muscle stimulation may therefore be facilitated by a too small distance from the septal lead tips. Therefore, we repositioned the leads more posterior and apical and after this re-intervention, the sensations disappeared.

Cardiac contractility modulation implantation and follow-up is a complex intervention that requires a good infrastructure (i.e. a specialized heart failure outpatient clinic). This is not only because the implantation procedure is longer than regular pacemaker implantations (due to haemodynamic measurement with left heart catheterization), but also because the potential for complications and interferences is greater due to the existing leads. Indeed, we observed a substantial acute complication rate in these patients with an important proportion of re-interventions for leads dislodgment. Moreover, device programming is more difficult than for a normal defibrillator setup; specialized training is needed. Far field sensing of the CCM signals from the ICD and possible false-positive defibrillator shock delivery has to be avoided. The CCM signal has to be delivered only during the absolute refractory period of the ICD. In our study, close control results in a complete absence of

this problem. At present, CCM can only be used in sinus rhythm or atrial stimulated patients. The large number of patients with chronic AF will not benefit from this procedure and as outlined in our cases series acute AF episodes may contribute to treatment failure and death.

Regarding the mid-term follow-up available in our series of very sick patients with terminal refractory heart failure (*Table 1*), we observed three sudden deaths and several other events (*Table 2*). Nevertheless, given the very high rate of hospitalizations and events prior to CCM implantation (*Table 1*), this rate could be expected. It may be possible that CCM needs more time to exert its full effect.⁹ The importance of sinus rhythm in CCM therapy was highlighted by two of the three patients who died due to EMD. Both had evidence of AF prior to death, thus limiting CCM delivery. Prophylactic amiodarone therapy should be considered because AF is a common event in CRT-NR (*Table 2*). Atrial fibrillation was a relapse of formerly known intermittent AF in all cases. Therefore, we think that the development of AF in CCM is not directly related to this form of therapy.

However, AF may lead to sudden loss of CCM augmentation and therefore may cause a negative rebound effect, which was also suggested from the results of cardiopulmonary exercise tests in the European randomized study. In this report, it was shown that in patients crossing from active to inactive CCM delivery peak oxygen uptake dropped below pre-randomization values.¹¹ In general, after CCM, our patients were in a somewhat better NYHA stage (62% were NYHA responders), had a better life quality after 3 months, and had a somewhat higher LVEF. However, BNP levels seemed to be unaltered (*Table 3*). In regard to the

Table 3 Changes after CCM implantation in 16 CRT-NR patients

Parameter	Pre CCM	3 month CCM	P-value
NYHA	3.4 ± 0.5	2.7 ± 0.4	<0.01
QOL	61 ± 20	33 ± 17	<0.01
LVEF (%) ^a	28.1 ± 7	31.3 ± 11	<0.03
Fractional shortening (%) ^a	15 ± 5	16 ± 4	NS
LVEDD (mm) ^a	7.50 ± 0.8	7.26 ± 0.9	<0.03
Mitral regurgitation ^a	2.57 ± 1	2.43 ± 1	NS
Tricuspid regurgitation ^a	2.14 ± 0.4	1.86 ± 1	NS
Brain natriuretic peptide ^a	1088 ± 738	1034 ± 550	NS

QOL, lower values are better, complete data set available for nine patients.

^aComplete data set available for 10 patients.

large amount of intracardiac material (6–10 leads), it should be noted that no complications can be attributed to this increase of foreign material. There were no signs of obstruction of the superior vena cava and of particular interest, tricuspid valve function was unaltered (Table 3). It seems unlikely that CCM improves prognosis in these very sick patients. Up to now we observed the death of three patients, all of them were sudden due to EMD. We have no indication that adverse effects of CCM stimulation may cause EMD directly; however, our observation should be investigated intensively.

Conclusion

We conclude that the CCM method is feasible and could be applied with calculated risks as a possible useful adjunct in CRT-NR when no other options are available. Mortality rate and clinical events remain high in this very sick population. Long-term prognostic studies need to be performed in a number of different heart failure groups in order to clarify more precisely the place of CCM in the armamentarium of modern cardiology and to define whether the observed effects warrant such a complicated and difficult procedure. Until more data from controlled clinical trials were available, there is no justification for adopting this technology on a routine basis. Multi-centre studies are under way to address these issues.

Limitations

This is only a preliminary report as only a limited number of patients have been studied with a relatively short follow-up time. Furthermore, the NYHA classification is a quite subjective measure of heart failure status. And finally, the results of echo measurements may be biased by the unblinded nature of its acquisition.

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Conflict of interest: H.N. received speakers honoraria from Impulse Dynamics.

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