Efficacy and survival in patients with cardiac contractility modulation: Long-term single center experience in 81 patients

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ABSTRACT

Aims: To analyze long-term efficacy and survival in patients with chronic heart failure treated with cardiac contractility modulation.

Methods: 81 patients implanted with a CCM device between 2004 and 2012 were included in this retrospective analysis. Changes in NYHA class, ejection fraction (EF), Minnesota Living with Heart Failure Questionnaire, NT-proBNP and peak VO$_2$ were analyzed during a mean follow up of 34.2 ± 28 months (6–123 months). Observed mortality rate was compared with that predicted by the MAGGIC Score.

Results: Patients were 61 ± 12 years old with EF $23 \pm 7\%$. Heart failure was due to ischemic (n = 48, 59.3%) or idiopathic dilated (n = 33, 40.7%) cardiomyopathy. EF increased from 23.1 ± 7.9 to $29.4 \pm 8.6\%$ (p < 0.05), mean NT-proBNP decreased from 4395 ± 3818 to 2762 ± 3490 ng/l (p < 0.05) and mean peak VO$_2$ increased from 13.9 ± 3.3 to 14.6 ± 3.5 ml/kg/min (p = 0.1). The overall clinical responder rate (at least 1 class improvement of NYHA within 6 months or last follow-up) was 74.1%. 21 (25.9%) patients died during follow up, 11 (52.4%) due to cardiac conditions and 10 (47.6%) due to non-cardiac conditions. Mortality rates at 1 and 3 years were 5.2% and 29.5% compared to mortality rates estimated from the MAGGIC risk score of 18.4% (p < 0.001) and 40% (p = ns), respectively. Log-Rank analysis of all events through 3 years of follow-up, however, was significantly less than predicted (p = 0.022).

Conclusions: CCM therapy improved quality of life, exercise capacity, NYHA class, EF and NT-proBNP levels during long-term follow up. Mortality rates appeared to be lower than estimated from the MAGGIC score.

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1. Introduction

Cardiac resynchronization therapy (CRT) improves heart failure symptoms, quality of life and exercise capacity and reduces hospitalizations and mortality [1,2] in patients with symptomatic systolic heart failure, severely depressed left ventricular ejection fraction (LVEF) and increased QRS duration [1,3]. However, the results of a study showed that patients with mechanical dyssynchrony detected by tissue Doppler imaging (TDI) but a normal QRS duration did not benefit from CRT [4]. These findings were confirmed by the results of the recently published EchoCRT Trial where patients with systolic heart failure and a QRS duration of less than 130 msec did not benefit clinically from CRT but even had a trend toward higher mortality [5]. Accordingly, currently published guidelines indicate a class I, level of evidence A recommendation only for patients with a QRS duration >150 milliseconds (ms) and a left bundle branch block (LBBB) [6]. Thus, QRS duration remains the primary selection criterion for CRT. Since approximately 60% of patients with heart failure have a normal QRS duration and at least 30% of patients receiving CRT do not respond, development of new device-based treatment options for patients with persistent symptoms despite optimal medical therapy (OMT) remains an important issue.

Cardiac contractility modulation (CCM) signals are relatively high intensity, nonexcitatory signals applied during the absolute refractory period that have been shown to enhance the strength of left ventricular (LV) contraction and improve exercise tolerance and quality of life. The mechanisms of action appear to involve effects on myocardial gene expression (including a reversal of several aspects of the fetal gene

program expressed in heart failure) and protein phosphorylation [7]. Two randomized trials demonstrated that CCM improves symptoms, quality of life and exercise capacity [8,9]. However, there are very limited data on long term survival in patients treated with CCM. In a recent published study from Schau et al. [10] long-term outcome in a cohort of 54 patients with CCM and severe heart failure was analyzed. In this cohort, the observed annual mortality rate was high (18.4%) but, nevertheless precisely matched the mortality predicted by the Seattle Heart Failure Model for that severe heart failure cohort. This suggested that CCM did not impact on mortality in this group of patients with severe, NYHA III–IV, heart failure. However, since CCM has been shown to improve exercise capacity, quality of life and LV size and function in NYHA II and III patients [11], it is hypothesized that CCM should improve mortality in the current cohort.

The purpose of this study was to evaluate the long-term effects of CCM on LV function, clinical status (NYHA class, exercise tolerance, quality of life and levels of NT-proBNP) and to provide insight into long term survival rate. For the later, we compared observed mortality to that predicted by the recently published score from the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) study [12]. The use of a model allows for estimation of mortality risk on a per patient basis from routine clinical data generally available for all heart failure patients, such as NYHA class, LVEF, medications, laboratory values and general medical history. Accordingly, the information required for calculation of this score can be reliably obtained for patients in a retrospective analysis.

2. Methods

2.1. Patient population

Eighty-one (81) consecutive patients with symptomatic heart failure and reduced left ventricular ejection fraction (LVEF) who were not indicated for CRT or, in case of an already implanted CRT-D device were considered CRT non-responders, were implanted with a CCM device (IMPULSE Dynamics, Orangeburg, NY, USA) between 2004 and 2012 after written informed consent. Patients were required to be on appropriate stable medical therapy for chronic heart failure including a beta-blocker, angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker and diuretics. Eighty (98.8%) of the patients had an already existing implantable cardiac defibrillator (ICD) or received one as a concomitant implant.

2.2. Implantation procedure

The Optimizer™ system consists of an implantable pulse generator (IPG), two right ventricular septal pacing leads and an atrial lead for sensing. In each case, the CCM device was successfully implanted under local anesthesia and conscious sedation. After right pectoral skin incision parallel to and with a distance of 2 cm to the clavicle a venous access through puncture of subclavian vein or cephalic vein cut down was achieved. Two ventricular screw-in leads (St Jude Medical Tendril 1388, 1788, 1888, 2088, 58–65 cm) were placed under fluoroscopic guidance in the right ventricular septum. Septal position was confirmed by left and right anterior oblique views. An atrial lead (St Jude Medical Tendril 1388, 1788, 1888, 2088, 52–58 cm) was fixed in the right atrium. In 30 patients LV dP/dt$_{max}$ measurements (Millar catheter) were made to confirm an acute increase in dP/dt$_{max}$ of at least 5% compared to baseline during application of CCM signals which was achieved in each patient with the first lead placement. After device implantation a cross-talk test was performed to exclude interference with the ICD.

During the study period, two different versions of the Optimizer™ device were implanted. The first 9 patients received an Optimizer™ II system with a fixed battery and longevity of approximately 12 months. After battery depletion generator exchange was required. The Optimizer™ III system introduced after the first 9 patients was rechargeable and all patients were upgraded. CCM signals were delivered at least 7 h per day with a range of 7–12 h per day depending on clinical response, underlying rhythm and current stage of heart failure. Therefore, the current cohort should generally be considered as 7 CCM hours per day cohort.

2.3. Study design

This was as a retrospective cohort study. All patients provided consent for anonymous analysis of standard clinical data. After implantation of the Optimizer™ system patients were followed per routine clinical practice at 3 month intervals. At each follow up visit, clinical assessments, including NYHA class, quality of life (Minnesota Living with Heart Failure Questionnaire, MLWHFQ) and NT-proBNP levels were obtained. In addition, echocardiograms and cardiopulmonary stress testing (for measurement of peak VO$_2$) were performed, based on clinical necessity, at variable intervals during the follow up period. For long term efficacy data, a minimum follow up period of 6 months was required.

Survival was analyzed independent of follow up time using Kaplan–Meier analysis. Cases of death were classified as either cardiac or non-cardiac.

The score from the MAGGIC meta-analysis was used to predict 1- and 3-year mortality rates for each patient. Briefly, this score consists of 13 baseline parameters including: age, gender, diabetes, chronic obstructive pulmonary disease, heart failure diagnosed within the last 18 months, current smoker, NYHA class, beta blockers, angiotensin converting enzyme inhibitor or aldosterone receptor blocker, body mass index, systolic blood pressure, creatinine, ejection fraction. The MAGGIC score was calculated for each patient using the calculator found at following link: http://www.heartfailurerisk.org/. Group average predicted survival was calculated as the average of the individual 1- and 3-year survival rates.

2.4. Statistical methods

All statistical calculations have been performed with the SAS system, release 9.3 (SAS Institute Inc., Cary, NC, USA) and IBM® SPSS®, release 20.0.0. Baseline characteristics, available for all participants, are presented as frequencies (absolute and relative) for categorical data and mean ± standard deviation for continuous data unless otherwise stated.

To test for changes in efficacy parameters (e.g., LV ejection fraction, NYHA, peak VO$_2$, MLWHFQ) during long term follow up, repeated measures ANOVA was performed. For these analyses the SAS procedure PROC MIXED has been used with patients' ID as a random variable and time points (baseline and last follow up) as fixed variable. We adjusted for follow up time in order to estimate the temporal influence on the outcome.

Survival curves were generated by the Kaplan–Meier method. Observed versus MAGGIC-predicted survival were compared using Log-Rank test for comparing the survival curves for the period of up to 3 years, and by a z-test for each time point of 1 year and 3 years. Since the MAGGIC model provides prediction for mortality rate only for 1 year and for 3 year time points, the Log-Rank test was applied by observing all actual events up to 1 year as a first time point and up to 3 years as a second time point, and by comparing to a simulated control group with similar initial number of patients (81), for which mortality events are generated for 1 year and for 3 years according to the MAGGIC predicted probability. The z-test was used to identify each of the time points that impact the differences between the groups from statistical standpoint.

3. Results

Baseline characteristics, summarized in Table 1, are typical for patients with advanced symptomatic heart failure. Patients were symptomatic with New York Heart Association (NYHA) class II (7.9%), III (77.8%) or IV (12.3%). Mean LV ejection fraction and peak VO$_2$ were significantly depressed, NT-proBNP was significantly elevated and quality of life (MLWHFQ) was dramatically impaired. All patients were in sinus rhythm at the time of implantation. Other baseline parameters contributing to the MAGGIC score are summarized in Table 1.

3.1. Clinical follow up

The mean follow up period was 34 (range 6 to 123) months. Twelve (12) patients developed persistent atrial fibrillation during follow up requiring electrical cardioversion and 3 patients developed permanent atrial fibrillation. In these 3 cases, the atrial spikes from the coexisting DR-ICD or CRT-D device (with atrial spikes induced by setting its parameters to under-sense atrial activity) were used to trigger CCM signals. In 12 patients, appropriate ICD shocks occurred for successful termination of VT/VF.

Four (4) patients had lead dislodgment or fracture with subsequent lead replacement. One patient required device removal and subsequent re-implantation for infection. Device replacements were required in 2 patients because of Optimizer™ III IPG malfunction. It is important to note that the reported event rate is total for the duration, and not per year. In comparison to the reported device related event rate of the randomized controlled trials (e.g. FIX-HF-5 feasibility and FIX-HF-5-pivotal) this event rate was no higher, and therefore consistent with their previous safety conclusion.

3.2. Efficacy outcomes

As summarized in Table 2, mean left ventricular ejection fraction increased during the follow up period from 23.1 ± 7.9 to 29.4 ± 8.6% (p < 0.05), left ventricular end-diastolic and end-systolic diameters decreased from 66.5 ± 7.7 and 57.9 ± 7.8 mm to 64.6 ± 8.9 and 54.8 ±

Table 1
Baseline clinical characteristics.

Characteristic	Mean (SD) or N (%)
Number of patients	81
Age (years)[a]	61.5 (12.0)
Male gender[a]	69 (85.2)
Body Mass Index (kg/m^2)[a]	29 (4.4)
LV ejection fraction (%)[a]	23.1 (7.9)
Systolic Blood Pressure (mm Hg)[a]	114 (17)
Heart failure etiology	
Ischemic cardiomyopathy	48 (59.3)
Dilated cardiomyopathy	33 (40.7)
NYHA functional class[a]	
I	0 (0)
II	8 (7.9)
III	63 (77.8)
IV	10 (12.3)
Creatinine (μmol/L)[a]	118 (40)
Diabetes[a]	32 (40)
Current smoker[a]	28 (35)
COPD[a]	17 (21)
CHF Diagnosis w/i 18 months[a]	79 (98)
QRS duration (msec)	112.0
Medication at baseline	
ACE inhibitor or ARB[a]	80 (98.8)
β-Blocker[a]	79 (97.5)
Loop diuretic	76 (93.8)
Aldosterone antagonist	45 (55.5)
Digoxin	21 (25.9)
Amiodarone	18 (22.0)
Implanted cardioverter-defibrillator (ICD)	
VR-ICD	48 (59,3)
DR-ICD	19 (23.5)
CRT-D	11 (13.6)
S-ICD	2 (2.5)
No ICD	1 (1.2)

ACE, angiotensin-converting enzyme; NYHA, New York Heart Association; ICD, implantable cardioverter defibrillator; VR-ICD, single chamber ICD; DR-ICD, dual chamber ICD; CRT-D, cardiac resynchronization therapy and ICD; S-ICD, subcutaneous ICD.
[a] Indicates that parameter is a component of the MAGGIC score.

9.2 mm, respectively (p < 0.05). Mean NYHA class improved from 3.0 ± 0.5 to 2.3 ± 0.9 (p < 0.05), mean NT-proBNP decreased from 4395 ± 3818 to 2762 ± 3490 ng/l (p < 0.05) and mean peak VO$_2$ increased from 13.9 ± 3.3 to 14.6 ± 3.5 ml/kg/min (p = 0.1). The overall clinical responder rate (defined as at least 1 class improvement of NYHA within 6 months or last follow-up) was 74.1%. Results of the repeated measures ANOVA (PROC MIXED) showed no time dependence of these findings.

3.3. Observed versus predicated mortality

During the follow up period, 21 patients (25.9%) died, 11 (52.4%) due to cardiac conditions and 10 (47.6%) due to non-cardiac causes. Kaplan–Meier survival curves are shown in Fig. 1. Comparing the

Table 2
Efficacy parameters at baseline and at follow up (mean and SD).

Parameter	Baseline	Long term follow-up	P
NYHA	3.0 (0.5)	2.3 (0.9)	0.001
MLHF, score	49.9 (17.7)	32.2 (18.2)	0.001
LVEF, %	23.1 (7.9)	29.4 (8.6)	0.001
LVEDD, mm	66.5 (7.7)	64.6 (8.9)	0.003
LVESD, mm	57.9 (7.8)	54.8 (9.2)	0.001
Peak VO$_2$, ml/kg/min	13.9 (3.3)	14.6 (3.5)	0.1
NT-proBNP, mg/dl	4395 (3818)	2762 (3490)	0.001
QRS duration, ms	112.0	112.8	ns

Abbreviations: NYHA, New York Heart Association; MLHF, Minnesota living with heart failure questionnaire; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; VO$_2$ peak, peak oxygen uptake; NT-proBNP, N-terminal pro brain natriuretic peptide.
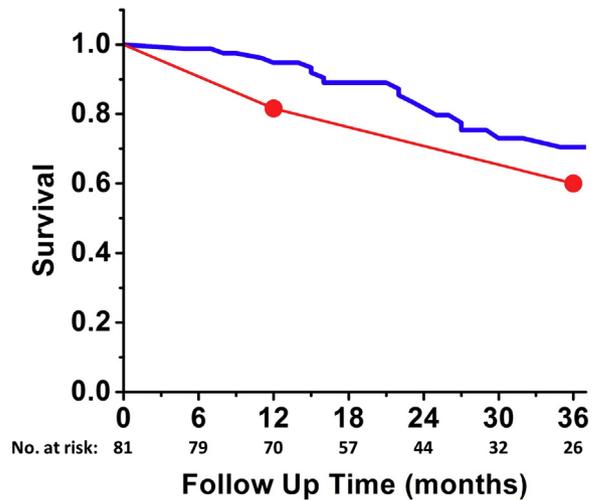

Fig. 1. Observed Kaplan–Meier survival curve (blue) compared to point estimates of survival at 1 and 3 years provided by the MAGGIC score. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

observed mortality rates with their respective predicted mortality rates derived from the MAGGIC score for the same patients, the results show observed 1 year mortality rate of 5.2%, which is statistically significantly (z = 4.68, p < 0.001) lower than the predicted mortality rate of 18.4%. A similar trend was seen in the observed 3 year mortality rate of 29.5%, compared with the predicted 40% (z = 1.15, p = ns, potentially due to the limited number of cases at that time point). The Log-Rank analysis for all events up to 3 years showed that patients treated by CCM had statistically significantly (X^2 = 5.22, P = 0.022) lower mortality rates as compared with the respective MAGGIC predicted mortality rates over a period of up to 3 years.

Two patients received successful cardiac transplantation after 172 and 611 days of CCM therapy and 1 patient received a left ventricular assist device after 1142 days.

An additional interesting observation is that the 10-year Kaplan–Meier survival exceeded 50%. Although the number of patients contributing to this result is small, it is an encouraging finding.

One limitation of the MAGGIC score is that it was predominantly based on data from the pre-ICD era and therefore does not fully account for the impact of ICD on survival, thus potentially over-estimating mortality rates of patients in our study. In order to address this limitation we calculated the Kaplan–Meier curve based on the composite of all-cause mortality and first events of VF or VT (as documented by ICD logs), assuming that every instance of VT or VF would have been a mortality event in the MAGGIC population. Kaplan–Meier survival curve of the composite events is shown in Fig. 2. The results yielded a 13.1% event rate in the study population compared to the 18.4% event rate predicted by MAGGIC at 1 year, and a 32.1% event rate in the study population
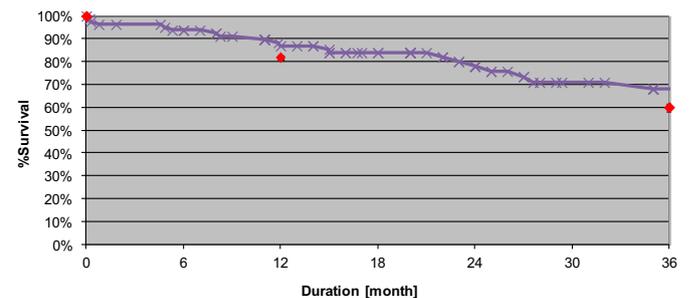

Fig. 2. Observed Kaplan–Meier survival curve of a composite endpoint of mortality and VT/VF events, compared to point estimates of survival at 1 and 3 years provided by the MAGGIC score.

compared to a 40.0% event rate predicted by MAGGIC at 3 years. Although with this extreme assumption and small number of patients the comparison is not statistically significant, it still provides consistent support for the positive trend of improvement in survival by CCM therapy.

3.4. Comparison of efficacy and mortality by etiology (ischemic versus non-ischemic)

There was no statistically significant difference with regards to efficacy parameters and mortality between ischemic and non-ischemic patients, thus accentuating that the underlying mechanism of action is not clearly affected by nearby scar or other etiology. We hypothesize that the effect is more likely by improving regional contractility, function and molecular expression, which then translate to reduction in stress and progressing reverse remodeling.

That reconfirms the independence of long-term effect from ischemic/non-ischemic etiology, and this is consistent with the findings of the large randomized efficacy trials with CCM that showed no substantial difference between ischemic/non-ischemic etiology [13].

The sub-groups have generally similar characteristics at baseline, i.e. no consistent trend across all parameters, and no statistically significant difference either. While both subgroups showed significant benefit in long term values vs. baseline values, it is difficult to conclude a specific trend of greater benefit in one group vs. the other across all measured efficacy values (Peak VO$_2$ and NYHA might seem better in the ischemic group while echo data, BNP and MLWHFQ might seem better in the non-ischemic group), probably due to the low number cases per group for efficacy evaluation. Similarly, it is difficult to conclude a specific trend between the two sub-groups with regard to survival, probably due to the low number of cases at risk per group for the Kaplan–Maier analysis. The current analysis shows that both 1 y and 3 y results with CCM appear lower than predicted, and while 1 y survival might seem better in the non-ischemic group, the 3 y survival might seem better in the ischemic group, and therefore the numbers are too low to properly identify any specific trend (Tables 3 and 4).

4. Discussion

The results of the current study provide the first evidence of long-term effects of CCM, demonstrating improvements in LV size and function, quality of life and exercise capacity. In addition, we observed reduced 1-year mortality and trends to reduce mortality at 3 years in comparison to mortality predicted by the recently established MAGGIC score.

The CCM therapy is indicated for use in patients with moderate to severe heart failure despite medical treatment. The experience to-date includes patients with NYHA classes II, III and IV symptoms, mostly with narrow QRS, but some also with wide QRS, after being treated by CRT. At present, the device can deliver the therapy to patients that are not in permanent atrial fibrillation, even though a preliminary experience with permanent AF was published recently showing the feasibility and clinical benefit in that population as well [14].

In the present cohort, we have observed short term and long-term clinical benefits throughout the range of cases treated by CCM, and could not yet derive a clear conclusion of a certain subgroup to show long-term benefit greater than others. This supports our view that CCM therapy is suitable for a broad range of heart failure cases with expected long term benefit. More data with larger cohort is warranted.

Our support of the potential benefit of CCM is consistent with the recent EHRA statement [15], which reviewed present potential therapies for this type of cohort and indicated that except for cardiac contractility modulation (CCM), no data based on randomized trials are available.

Transitions in NYHA over time were analyzed and are shown in Table 5. 3 (37.5%) of the 8 patients with baseline NYHA 2 improved while 1 (25%) was deteriorating over long-term follow-up. 40 (63.5%) of the 63 patients with baseline NYHA 3 improved while 6 (9.5%) were deteriorating over long-term follow-up. 9 (90%) of the 10 patients with baseline NYHA 4 improved over long-term follow-up.

It should further be noted, that based on the findings of the FIX-HF-4 study (NYHA II–III) and the FIX-HF-5 study subgroup analysis (NYHA III, EF > 25%), it appears that the earlier in the disease progression that CCM is being offered, the greater is the expected clinical benefit. This observation is not aimed to exclude patients from being treated, but rather to increase the awareness to the potential substantial benefit and mitigation of deterioration provided by the therapy, and therefore, the authors speculate that the best candidates for therapy are those that are not indicated for CRT (i.e. no LBBB or QRS > 150), preferably in NYHA II–III symptoms and EF in the range of 20–45%.

A prior multicenter, randomized, double blind, double crossover study of CCM in 164 heart failure patients with NYHA Class II or III symptoms despite optimal medical therapy and LVEF < 35% (the FIX-HF-4 study) demonstrated clinically significant improvement in peak oxygen consumption and MLWHFQ with 3 months of CCM treatment [8]. The largest study of CCM to date was a multicenter study involving 428 patients recruited from 50 sites in the US (FIX-HF-5 study) [9]. After 6 months of therapy, the mean change in peak VO$_2$ was 0.7 ml/kg/min greater in treatment than control group (p = 0.024), though ventilatory anaerobic threshold (the declared primary endpoint) did not improve. MLWHFQ also improved by 9.7 points more in treatment than control

Table 4
Long-term mortality by etiology.

Parameter	N at Baseline	N at follow-up	Mortality	MAGGIC	CCM
Ischemic	48	42	Mortality 1 y	20.1%	8.6%
			Mortality 3 y	43.0%	26.5%
Non-ischemic	33	29	Mortality 1 y	15.9%	0.0%
			Mortality 3 y	35.6%	36.1%
All	81	70	Mortality 1 y	18.4%	5.2%
			Mortality 3 y	40.4%	29.5%

Table 3
Long-term efficacy parameters by etiology.

Parameter	LVEF (%)	LVESD (mm)	LVEDD (mm)	MLWHFQ (score)	NT-proBNP (mg/dl)	Peak VO$_2$ (ml (kg/min)	NYHA
Baseline							
Ischemic	24.13	56.43	65.18	48.59	4216.38	12.74	3.06
Non-ischemic	21.67	59.45	67.24	51.83	4520.57	14.70	2.97
Mean change							
Ischemic	4.64	−2.38	−1.92	−13.77	−1279.42	0.85	−0.77
Non-ischemic	8.81	−4.09	−1.90	−21.83	−2117.37	0.50	−0.61
Pval FU vs. BL							
Ischemic	0.00022	0.03789	0.02624	0.00018	0.01231	0.20355	0.00000
Non-ischemic	0.00003	0.00601	0.05497	0.00001	0.02817	0.31229	0.00310

Abbreviations: LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVEDD, left ventricular end-diastolic diameter; MLHF, Minnesota living with heart failure questionnaire; NT-proBNP, N-terminal pro brain natriuretic peptide. VO$_2$ peak, peak oxygen uptake; NYHA, New York Heart Association.

Table 5
Transitions in NYHA over time.

		Long term NYHA (% per baseline NYHA)			
		1	2	3	4
Baseline NYHA	2	3 (38%)	3 (38%)	1 (13%)	1 (13%)
	3	11 (17%)	29 (46%)	17 (27%)	6 (10%)
	4	0 (00%)	3 (30%)	6 (60%)	1 (10%)

(p < 0.0001). The primary safety endpoint, a non-inferiority comparison between groups at 12 months of the composite of all-cause mortality and all cause hospitalizations (12.5% allowable delta) was also met. In a prespecified subgroup consisting of patients with LVEF ≥ 25% and NYHA class III symptoms, the mean change in VAT was 0.64 ml/kg/min greater (p = 0.03), peak VO_2 was 1.31 ml/kg/min greater (p = 0.001) and MLWHFQ was 10.8 points better (p = 0.003) in the treatment group than in the control group [13]. Interestingly, peak VO_2 in the treatment group increased by 0.25 ml/kg/min compared with a 1.06 ml/mg/min decrease in the control group. This suggests that CCM largely preserves the patients' clinical exercise tolerance in the face of an otherwise progressive and significant decline that is apparent in as little as 6 months. Although baseline characteristics were slightly different, our study also consisted predominantly of NYHA III symptoms with average LVEF of almost 25%. We demonstrated similar efficacy effects in peak VO_2 and MLWHFQ over longer periods of time.

Moreover, observing the evolution of the peak VO_2 changes from baseline by sub-grouping the cohort according to length of follow-up, it appears that patients with treatment periods ranging between 6 and 24 months had improvement of 0.53 ml/kg/min (N = 41) while those with 24 to 48 months follow up had improvement of 1.95 ml/kg-min (N = 24, P = 0.027). This suggests that the positive effects of CCM build up over time, become substantial and sustained over long time periods.

With regards to survival, a recent published study by Schau et al. in 54 patients with a mean LVEF of 23% demonstrated a 1 year mortality rate of 18.4% which was precisely predicted by the Seattle Heart Failure Model but less than the 28% predicted by the Heart Failure Survival Score. Observed mortality in that study was significantly greater than in our study. A significantly lower baseline peak VO_2, higher baseline NT-proBNP levels, higher proportion of NYHA IV patients and the lack of an ICD in 21% of patients might contribute to that difference.

It should be noted that the mortality rates in this study are slightly higher than reported in the previous randomized controlled studies. The reason for that is that this population has a blend of narrow QSR patients and wide QRS patients that did not respond to CRT, and therefore have worse prognosis at baseline.

A meta-analysis from Kwong et al. [16] combining data from 641 patients from 3 randomized trials suggested that CCM did not significantly improve all-cause mortality (n = 629, RR 1.19, 95% CI 0.50–2.86, P = 0.69) at 1 year, nor was there a favorable effect in all-cause hospitalizations. However, this meta-analysis had several potential limitations since it was based on published manuscript analysis only and was not based on individual patient data. Further, there were no data on peak VO_2 or NYHA class included in that analysis to provide a basis for overall comparison of patient populations.

A later meta-analysis by Giallaria et al. analyzed the individual records of the 641 cases, and concluded that CCM significantly improved Peak VO_2, 6-minute walk and quality of life measured by Minnesota Living With Heart Failure Questionnaire (MLWHFQ) [17].

Eleven (11, 13.6%) of the patients in our study had a CRT-D at the time of the CCM system implantation. Although too small group of patients to make firm conclusions, our findings are consistent with this case report by Butter et al. [18] and a case series reported by Nagele et al. [19], in that application of CCM in CRT responders was feasible, there were no significant safety concerns, and clinical improvements were observed. A specific, larger scale study looking at CCM in CRT non-responders is warranted.

4.1. Study limitations

This was a small, single-site, retrospective analysis with no randomized control group. Mortality data were compared to mortality estimated from a recently published heart failure survival model. The MAGGIC integer score was derived from approximately 40,000 patients included in 30 studies spanning a very wide range of clinical conditions. The parameters of the MAGGIC score are readily available and therefore easy to apply, especially in a retrospective study. Use of such validated predictors of mortality have become helpful in providing insights into effects of therapies, especially in small studies and when long term randomized studies are not yet available. Use of such models, however, must be with the understanding of their limitations. For example, there might be differences in current applicable guidelines compared with those of the time period from which the model's data was derived. Such is the case with the MAGGIC score, which is mainly derived from clinical trial results from the pre ICD era. To address this issue, we made a conservative assumption that any episode of VT or VF detected by our patients' ICD equated with a death. The Kaplan–Meier survival determined under these conditions was still better than predicted by the MAGGIC score, providing further support for the premise that CCM improves survival.

An additional limitation of this study is the retrospective design of the study. Therefore, there were varying durations of follow up. However, a statistical analysis of time dependence of efficacy parameters (PROC MIXED) revealed no significant association between follow up time and efficacy outcome.

Changes of medication, e.g. addition of aldosterone-inhibitors or ivabradine were at the discretion of the treating physicians and might influence overall clinical status. However, neither of these drugs is known to impact on quality of life or exercise tolerance.

Finally, due to algorithmic limitations, CCM signals can be applied only in patients who are in sinus rhythm. In patients with persistent atrial fibrillation electrical or medical cardioversion or ablation is required to restore sinus rhythm. In 3 patients with the occurrence of permanent atrial fibrillation the spike of the atrial lead of the concomitant DR-ICD or CRT-D with programmed atrial under-sensing could be used to trigger CCM signals. However, in patients with inhibition of CCM therapy due to atrial fibrillation, clinical deterioration was observed (either due to the effects of atrial fibrillation or to cessation of CCM signal), which was reversed after restoration of sinus rhythm.

5. Conclusions

Patients with chronic heart failure treated with Cardiac Contractility Modulation had a significant improvement in left ventricular size and function, quality of life, NYHA class, peak VO_2 and decreased levels of NT-proBNP during long-term follow up. The overall responder rate in terms of improvement of at least 1 NYHA class was 74.1%. Taking the limitations of this study into account, the results indicated that in a heart failure population with moderate-to-severe heart failure treated with CCM, mortality rates are lower than predicted by the MAGGIC integer score. When viewed in the context of all data in the literature, the present study provides additional evidence that cardiac contractility modulation is safe and effective for treatment of chronic heart failure with reduced left ventricular ejection fraction.

Conflict of interest

J Kuschyk has received modest speaker fees from IMPULSE Dynamics. D Burkhoff is a consultant to IMPULSE Dynamics. B Rousso is an employee of IMPULSE Dynamics. M Borggrefe receives speaker's fee from Impulse Dynamics and serves on their International advisory board.

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