Long-term survival with Cardiac Contractility Modulation in patients with NYHA II or III symptoms and normal QRS duration

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ABSTRACT

Aims: Cardiac Contractility Modulation (CCM) is a treatment for heart failure based on electrical signals applied during the absolute refractory period. CCM improves myocardial molecular and biochemical characteristics of heart failure and improves exercise tolerance and quality of life. However, the long term impact on survival has not been described.

Methods and results: Survival was determined retrospectively from a cohort of 68 consecutive heart failure cases with NYHA II or III symptoms and QRS duration ≤130 ms, implanted with a CCM device between May 2002 and July 2013 in either Bochum or Ludenscheid, Germany. Results were compared with predicted survival (Seattle Heart Failure Model; SHFM) pre-implant for each patient. Mean follow-up was 4.5 years (range 0.25–10.3 years). Baseline characteristics were as follows: mean age 61 years, 88% male, 68% with ischemic heart disease, 78% with an ICD, mean NYHA class 2.9 ± 0.3, LVEF $26\% \pm 6\%$ (range 15–40%) and mean QRS duration 106 ± 11 ms. Mortality rates (Kaplan–Meier analysis) at 1-, 2- and 5-years were lower with CCM than predicted by SHFM for the cohort (0% with CCM vs. 6.1% per SHFM, 3.5% vs. 11.8%, and 14.2% vs. 27.7%, respectively, p = 0.007).

Conclusions: Long-term mortality rates in heart failure patients with NYHA (II–III) and QRS ≤ 130 ms are lower when treated by CCM than predicted for the cohort. These findings warrant substantiation in a prospective study.

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1. Introduction

Cardiac Contractility Modulation (CCM) is a treatment for heart failure employing relatively high intensity electrical signals applied during the absolute refractory period [1,2]. Animal studies [3] suggest that CCM treatment acts chronically to normalize myocardial mRNA expression of genes associated with heart failure and to reverse cardiac remodeling. CCM has been shown to improve myocardial molecular and biochemical abnormalities pathognomonic of heart failure and to improve exercise tolerance, ejection fraction (EF), symptoms and quality of life [4].

Among the clinical studies, three main randomized controlled studies have evaluated the therapy's safety and efficacy with endpoints related to exercise capacity by cardio-pulmonary stress test and by 6-minute walk test, and to quality of life by MLWHFQ and by NYHA class (the FIX-CHF-4 study, 164 patients, crossover 3 + 3 months follow-up, in Europe; the FIX-HF-5-feasibility study, 49 patients, 6 months follow-up, in USA; and the FIX-HF-5 study, 428 patients, 6 months follow-up, in USA). Several publications cover the results and provide detailed review [2,13] and meta-analysis [15,16].

The short term randomized double blind crossover study (FIX-CHF-4) involving 164 patients with moderate to severe heart failure (NYHA II or III, EF < 35%, narrow QRS, Peak VO2 ≥ 10 mL/min/kg) [5] showed that three months of CCM treatment significantly improved exercise capacity, as measured by peak VO2 in cardiopulmonary stress test and by 6 minute walk distance, and quality of life, as measured by Minnesota Living With Heart Failure Questionnaire (MLWHFQ) and NYHA classification.

Long term follow up of patients with CCM was described by Schau et al. [6] in 54 patients with severe congestive heart failure treated with CCM. Although no difference in observed and predicted mortality was observed over an average of 21 months, that study was not powered to show a survival benefit, and the severity of heart failure at baseline was high (NYHA III–IV, mean Peak VO2 of 10.0 ± 4.8 mL/min/kg) compared with the typical patient treated with CCM. Additional retrospective long term follow-up (mean follow-up 34 months) was performed by Kuschyk et al. [7], which included a cohort of 81 patients with mixed characteristics, from NYHA class II to IV level of symptoms, mostly normal and a few wide QRS cases, and mean EF of 23.1. That cohort had better baseline characteristics than the cohort by Schau et al., and showed long term benefit in efficacy endpoints, and improved survival vs. MAGGIC prediction survival prediction model. One limitation of the MAGGIC score (relative to the SHFM score) is that it was partially based on data from the pre-ICD era and therefore does not fully account

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for the impact of ICD on survival. Likewise, the heterogeneous population studied by Kuschyk et al. had relatively worse baseline condition compared with the baseline characteristics of the previously studied cohort in the FIX-CHF-4 randomized study.

It should be noted that subgroup analysis of the FIX-HF-5 prospective randomized trial indicated greater improvement with CCM in patients with less severe CHF [8,14].

Since the authors have participated in the FIX-CHF-4 study, and most of the subsequent experience gained by the authors in routine treatment with CCM is with similar patient characteristics, we therefore examined whether a long-term mortality benefit from CCM would be observed in patients with less severe heart failure. For comparative purposes, the current study examined outcomes for patients with similar characteristics as those enrolled in FIX-CHF-4, with the primary endpoint being all-cause mortality in long term follow-up compared with the SHFM mortality risk score.

2. Methods

2.1. Patients

Baseline characteristics of all patients treated with CCM were screened, and 68 met the criteria of having NYHA II or III Symptoms (5 patients NYHA II, 5 patients NYHA IIb, 58 patients NYHA III) and normal QRS duration. The study retrospectively analyzed outcomes in those 68 patients who underwent implantation of an Optimizer™ system (Impulse Dynamics, Orangeburg, NY, USA) in Bochum or Ludenscheid between May 2002 and July 2013. Relevant patients were on a guideline-appropriate, stable medical treatment for heart failure (diuretics 88%, ACEi/ARB 91%, beta-blockers 91%, and aldosterone-blockers 47%) and had a QRS width less than or equal to 130 ms (mean 106 ms). Patients received CCM only if they had no recent myocardial infarction (within 3 months), clinically significant angina, or hospitalization for heart failure requiring intravenous treatments within 30 days.

Patients included in this analysis had baseline characteristics (Table 1) similar to those in the FIX-CHF-4 study [5] (NYHA II–III, mean EF of 26.3 ± 6.1, by echocardiography, Peak VO2 ≥ 10 mL/min/kg), which are less symptomatic relative to cohorts in other CCM trials.

Baseline characteristics were obtained from the medical records at the time of implant. Outcomes assessment was performed during routine follow up clinical visits for the device with live or dead status and date of death, if applicable. The Ethics Committee approved this retrospective analysis.

2.2. Methodology and device treatment

CCM therapy is delivered as a non-excitatory electrical signal applied during the absolute refractory period. The signal is applied after the device senses local activity of the tissue, with criteria defined to determine proper timing of the signal delivery and avoid delivery during ventricular arrhythmias. The implant procedure is routine in the medical two centers. Details of CCM signal delivery have been detailed previously [5,8]. Briefly, the Optimizer™ system consists of an implanted pulse generator, as the current model shown in Fig. 1, and three pacing leads (a standard right atrial lead and two active fixation leads placed at the septum of the right ventricle). Fig. 2 shows a chest X-ray of an implanted Optimizer system. Acute contractility was evaluated during implant by using a Millar Tip catheter for LV pressure measurement and repositioning of the ventricular leads was performed if needed. Typically, CCM activation produced an acute increase in LV dP/dt of about 10%. CCM was programmed to deliver impulses for 7 h per day, intermittently, by one hour of CCM activity approximately every 3 h.

Patients treated with CCM therapy are followed routinely at the medical centers, every 6 months. During the follow-up visit the device is interrogated and the signal delivery parameters are checked. The follow-up visits take place in an outpatient setting, and the patients

Table 1
Patient demographic data at implantation.

	n (%) or mean + std
Age (years)	61.0 ± 10.7
Gender	
Male	60 (88%)
Female	8 (12%)
Weight (kg)	86.2 ± 15.3
BMI	28.8 ± 4.5
Systolic BP (mmHg)	123.9 ± 17.6
ICD	53 (78%)
Ischemic cardiomyopathy	46 (68%)
Dilated or non-ischemic cardiomyopathy	22 (32%)
Diabetes	30 (44%)
QRS (ms)	106.3 ± 11.0
NYHA	2.89 ± 0.28
NYHA II	5
NYHA IIb (NYHA II–III)	5
NYHA III	58
LVEF	26.3 ± 6.1 [range 15–40]
Medication	
Digoxin	17 (25%)
ACE-I or ARB	62 (91%)
Beta blocker	62 (91%)
Statins	43 (63%)
Allopurinol	13 (21%)
Aldosterone blocker/eplerenone/spironolactone	32 (47%)
Diuretics	60 (88%)
Baseline lab tests	
Sodium [mmol/L]	139.37 ± 3.74
Creatinine [mg/dL]	1.27 ± 0.41
Hemoglobin (HgB) [g/dL]	13.60 ± 1.49
Lymphocytes [%]	22.56 ± 5.58
Uric acid [mg/dL]	7.58 ± 1.03
Total cholesterol [mg/dL]	181.5 ± 28.6
BNP [pg/ml]	570.4 ± 588.1
NT-proBNP [pg/ml]	1875.1 ± 2634.8
History of an AF event	13 (19%)
COPD	8 (12%)
Smoker	24 (35%)
Heart failure diagnosed within the last 18 months before implant	18 (22%)

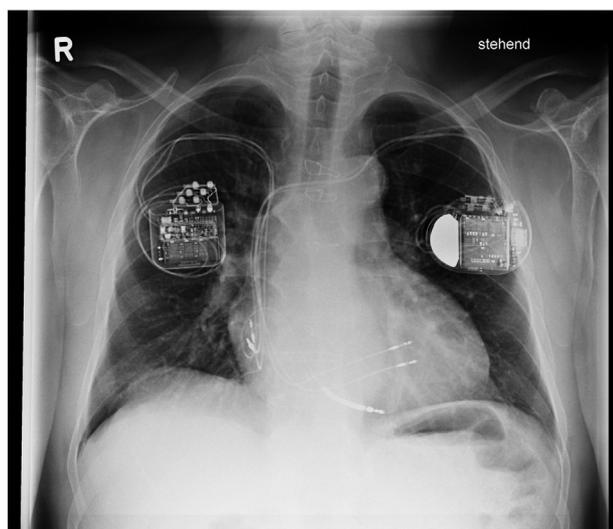**Fig. 1.** The Optimizer IVs implantable pulse generator.

Fig. 2. Chest X-ray image of an implanted Optimizer system. The image shows a DDD-ICD implanted on the left side with a single-coil electrode positioned at the RV apex, and the Optimizer IPG implanted on the right side with an atrial electrode and 2 ventricular electrodes positioned at the RV septum.

are also being clinically evaluated. The medical records of the patients were updated accordingly. Information about mortality was collected based on scanning the medical records, and if necessary for additional data contacting the local physician.

2.3. Statistical analysis

The Seattle Heart Failure Model (SHFM) was used to calculate projected survival rates. SHFM is a validated scoring system used to estimate survival in patients with heart failure [9,10] based on a number of clinical parameters including NYHA class, gender, age, systolic blood pressure, CAD, LVEF, medication, lymphocyte count, cholesterol, uric acid and hemoglobin. In cases where some lab test results (uric acid, and to some extent lymphocyte count, and cholesterol) were missing, imputation was applied using the mean value of the cohort in that medical center. Sensitivity analysis of the imputed values showed that the impact of standard deviations in these specific values has minimal impact on the predicted mortality for the present cohort.

SHFM was calculated from baseline characteristic of each patient before implant and mean SHFM scores provided the predicted probability of survival at 1, 2, and 5 years for the cohort. To compare the predicted survival to actual survival we constructed a Kaplan–Meier curve for the observed cohort. Statistical difference between the Kaplan–Meier curve and the predicted survival probabilities was tested using a one sample log rank test which aggregates the discrepancy between observed and expected deaths at the three time points [19].

3. Results

The cohort of 68 patients was followed up over a period of up to 10.3 years (mean 4.5 years). Sixteen deaths occurred in this patient cohort over this follow-up period, six of them were characterized as cardiovascular-related by the treating physician. In 2 patients the CCM therapy was stopped, one after 6 months due to need for an LVAD and one after 9 months due to no apparent improvement, and therefore these cases were censored in the analysis at those time points accordingly.

The predicted survival rate was calculated using the SHFM model and actual survival with CCM therapy was described using Kaplan–Meier analysis. SHFM risk scores were calculated per patient according to the individual's baseline characteristics, and the mean values for the cohort were calculated. The resulting comparison of the Kaplan–Meier curve and the SHFM predicted mortality is depicted graphically in Fig. 3.

For the group as a whole, SHFM predicted 1-, 2- and 5-year mortality rates were 6.1%, 11.8% and 27.7%, respectively. Observed mortality rates with CCM therapy at these same time points based on Kaplan–Meier analysis were 0%, 3.5% and 14.2%, respectively. Observed mortality was significantly lower than predicted mortality ($\chi^2_1 = 7.42$, p = 0.007).

4. Discussion

The major finding of this study is that use of CCM is associated with less all-cause mortality compared to the predicted mortality of similar patients treated with medications and standard device care alone. This retrospective benefit was observed in patients with less severe CHF (moderate reductions in EF and earlier NYHA status) and without QRS prolongation. The mortality benefit was observed as early as 1 year after onset of treatment and lasted throughout the observation period of 5 years. These data suggest that CCM may have additive benefit to a standard medical regimen. The improvement was substantial, suggesting that CCM may provide substantial long term clinical benefit to patients with moderate degrees of heart failure.

The SCD-HeFT study [15] evaluated mortality rates in a similar population (NYHA II and III heart failure patients), and observed a 5-year mortality rate with ICD of 28.9%. For the present cohort, SHFM predicted a similar 5-year mortality rate of 27.7%. These data confirm that the observed mortality rates with CCM are lower than expected in similar population without CCM.

The recently published PARADIGM-HF study [16] has followed patients with similar heart failure condition (mostly NYHA II–III, mean EF 29.5%) and has also shown ~24% to ~28% (treatment vs. control) all-cause mortality in the Kaplan–Meier curves at 3.5 years. Although the current cohort is small, and the observation is retrospective, this comparison again suggests that the observed all-cause mortality rate with CCM seems lower than expected in similar population without CCM.

There are a variety of alternative medical and device treatments for patients with symptomatic heart failure. However eligibility limits their broad use. For example a significant number of symptomatic heart failure patients are ineligible for cardiac resynchronization therapy (CRT) [11,12] due to narrow QRS complexes. Marked reactive airways disease or conduction disorders can limit use of beta-adrenergic blockers. Renal dysfunction is a relative contraindication for the use of ace-inhibitors, angiotensin receptor blockers, or aldosterone antagonists. Positive ionotropic drugs have not been demonstrated to improve
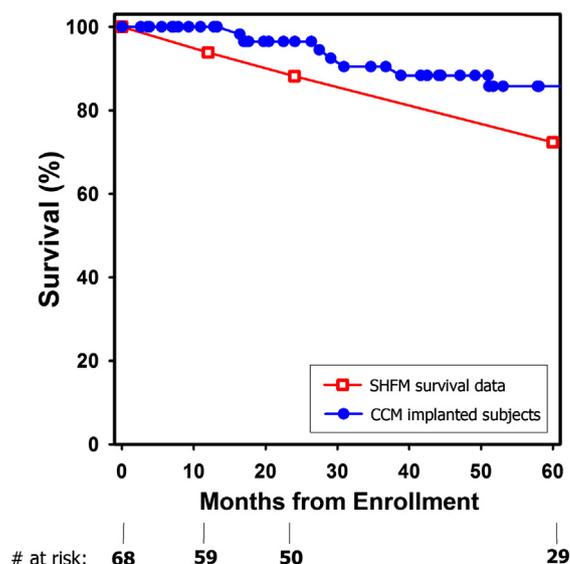

Fig. 3. Kaplan–Maier curve for the survival of CCM treated patients compared with the SHFM predicted survival based on the cohort's baseline characteristics.

long-term mortality; which may often worsen it due to increases in myocardial oxygen demand.

Clinical improvement has been shown to be similar between CCM (for narrow QRS patients) and CRT (for patients with LBBB/wide QRS) [14]. Moreover, cardiac efficiency improves without an increase in myocardial oxygen consumption both with CCM and with CRT.

In the FIX-CHF-5 study, the safety and efficacy of CCM over six months was examined in 428 randomized patients with moderate to severe heart failure (NYHA functional class III/IV), narrow QRS, on optimal medical treatment (OMT). In a secondary subgroup analysis [13], patients with less severe symptoms and higher EFs (≥25%) benefitted more from CCM than the full cohort of patients with lower EF (<35%). Generally, the patient population of the FIX-HF-5 study had more advanced heart failure than in the present cohort, which explains the difference in overall number of events compared with the FIX-HF-5 study. An important feature of this study is that it provides long term follow up in a cohort of heart failure patients treated with CCM (mean 4.5 years ranging up to 10 years), while the FIX-HF-5 study did not measure outcomes beyond one year.

The current study shows substantially better than predicted long term outcome in subjects with less severe CHF receiving CCM. There are several potential mechanisms to explain this observation. First, CCM therapy has an impulse activation range of a few centimeters around the electrodes and if the volume of dysfunctional cardiac tissue is too large, as with severe left ventricular dilatation and low EF, the immediately affected area by CCM will be smaller and potentially less effective in remodeling, restoring function and improve outcomes. Second, CCM improves mRNA expression and protein expression of genes associated with heart failure [2,3]. These are likely to be effective when there is sufficient viable myocardium, and thus more likely to show greater improvement at earlier stage of the disease. Third, CCM might work through mechanisms distinct from those producing improved contraction, and Peak VO2, and MLWHFQ benefits. It is hypothesized that such a mechanism could potentially involve inhibition of arrhythmias due to electrical remodeling (e.g. by normalization of SERCA2a functionality and gap junction expression [2,3]), or improved regional contractility sufficient to reduce neuro-hormonal stress and prevent moderate heart failure from progressing.

Prior studies have demonstrated improvements in functional status following CCM, both short and long term. However despite these improvements and associated safety, it has not yet been prospectively demonstrated in a randomized trial that CCM treatment improves long term survival. Much of the reason is related to the small number of subjects enrolled in prior studies which were primarily designed to assess VO2 and functional status.

Two meta-analyses were performed on the results of the past randomized studies. The Kwong et al. meta-analysis [17] related to the mortality and hospitalization data as available from prior journal publications. Since none of the randomized trials was powered for prospective mortality analysis, and all were with short follow-up periods (3–12 months), it was unable to draw conclusion regarding survival. In contrast, the present retrospective observation is based on long-term data and therefore provides meaningful insights. The Giallauria et al. meta-analysis [18] looked at clinical evaluations and included analysis based on a per-patient individual record, which enables proper statistical analysis. The Giallauria et al. meta-analysis showed that CCM significantly improved Peak VO2, 6-minute walk distance and quality of life. These have been established to be associated with prognosis, thus consistent with the present findings. The results of the current retrospective study support the need for a prospective randomized trial to assess the effects of CCM on mortality, especially in those patients with moderate heart failure.

4.1. Study limitations

The present study is based on a retrospective analysis, from two medical centers, over a long time period, involving a limited number of patients. These factors combine to impose a natural bias influencing outcomes. Medication compliance was not assessed throughout the follow up thus changes in medication use could have potentially influenced the results; especially since several medications (beta-blockers, ACEi/ARBs, and aldosterone antagonists have a demonstrated impact on mortality). This concern is minimized since all patients had demonstrated regular use of the same medications prior to implantation.

It is acknowledged that there may be a selection bias in the choice of patients who were implanted with the Optimizer system depending on the treating physician decision. While the rationale for defining the criteria was explained in the background for having baseline characteristics similar to those in the FIX-CHF-4 study, this choice of criteria may add further selection bias. It is also acknowledged that the optimal way to derive conclusions would be through a properly conducted randomized placebo-controlled trial.

The use of historical controls from based on cohorts of other studies in other sites (SHFM) may introduce variability, especially if there is hidden bias that may apply to certain sites or patient selection or treatment procedures that is not modeled by the comparator control.

On the other hand, the extensive characterization of the SHFM population may allow for a better comparison with the current cohort than a matched-control approach where the degree of documentation and rigor of follow up might be less robust.

The Seattle Heart Failure Model was developed and validated among outpatients participating in clinical trials, observational studies, or clinical registries, and may not be generalizable to hospitalized patients or those with major life-altering comorbidities such as cirrhosis, renal failure, dementia, or cancer. The estimated benefit for medications was based on the doses used by patients in clinical trials, and effects may be different if higher or lower doses are used. More generally, the SHFM performed extremely well in all 5 cohorts in which it was validated, however, as in any model, there could be differences from new cohorts that are characterized by parameters that were not modeled. These differences might be influence the prognosis, or the accuracy of the prediction.

Being a retrospective observational study, the authors could effectively analyze all-cause mortality and cardiovascular mortality data. However, hospitalizations data could have been of interest as well, but impractical to collect over such a long follow-up period of up to 11 years, as patients tend to be admitted to various hospitals, and not just at the implanting medical centers, therefore made it difficult to trace historical records from other hospitals. In addition, no comparator was available for such data. Such data is warranted form future prospective studies.

5. Summary

The present study demonstrates a lower mortality rate in patients with moderate heart failure treated with CCM plus optimal medical care versus the predicted mortality rates with optimal medical care alone. The reduction in mortality occurred after one year and persisted for at least 5 years. CCM may play an important role in the treatment of patients with normal QRS duration and moderate heart failure. Further data from prospective randomized trials is warranted.

Acronyms

ACEi   angiotensin converting enzyme inhibitor
ARB   angiotensin receptor blocker
CCM   Cardiac Contractility Modulation
CRT   cardiac resynchronization therapy
EF   ejection fraction
OMT   optimal medical therapy
SHFM   Seattle Heart Failure Model
Peak VO$_2$ maximal oxygen consumption (in cardio-pulmonary stress test)
NYHA   New York Heart Association classification

Conflict of interest statement

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