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CLINICAL RESEARCH

Long-term outcome of cardiac contractility modulation in patients with severe congestive heart failure

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Aims Cardiac contractility modulation (CCM) is a new form of electrical therapy in patients with congestive heart failure. Recently published clinical studies provide evidence of safety and improvements of exercise tolerance and quality of life. In this study, we investigated the impact of CCM on cardiac and all-cause mortality.

Methods and results Fifty-four consecutive patients (age 63 ± 10 years, 91% male, left ventricular ejection fraction 23 ± 6%, baseline peak oxygen consumption 10.0 ± 4.8 mL/min/kg, N-terminal pro-B-type natriuretic peptide 5194 pg/mL, New York Heart Association III/IV) who underwent implantation of an Optimizer™ system (IMPULSE Dynamics, Orangeburg, NY, USA) at our centre between June 2003 and June 2010 were analysed retrospectively. Patients were followed every 3 months at our outpatient clinic. This study determined long-term outcomes of patients receiving CCM therapy. Twenty-four (44%) patients died during the follow-up period, which included 19 cardiac deaths (3 sudden cardiac deaths and 16 terminal cardiac pump failure deaths). The Kaplan–Meier analysis calculated a median survival time of 992 days (33.1 months) and a mean death rate of 18.4% per year. All-cause mortality for these patients was precisely predicted by the Seattle Heart Failure Model.

Conclusion Cardiac contractility modulation appears to be a safe therapeutic option for advanced heart failure patients who have no other therapeutic options. Symptomatic improvement by CCM has been shown in earlier studies but our observational study suggests, for the first time, that there is no adverse effect of CCM on long-term survival.

Keywords Congestive heart failure • Prognosis • Cardiac contractility modulation

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Introduction

Cardiac contractility modulation (CCM) is an electrical method of enhancing ventricular contractile strength that was introduced for treating patients with chronic heart failure (CHF) independent of the synchrony of myocardial contraction.[1,2] Studies indicate that CCM signals can enhance contractile performance acutely,[1–3] principally by enhancing phosphorylation of key proteins, especially phospholamban and, in the long term, normalizes myocardial gene programmes and initiates reverse remodelling in animal models and in patients with heart failure.[4]

Cardiac contractility modulation signals are delivered 30–40 ms after detection of local myocardial activation during the absolute refractory period. Thus, although the amount of energy delivered during a CCM pulse is nearly 100 times higher than during a standard pacemaker impulse, these signals do not initiate a contraction, do not recruit additional contractile elements, and do not modify myocardial activation sequence. No additional action potential is initiated, as observed with paired pacing or post-extra systolic potentiation.

Initial non-randomized clinical studies with short-term application of CCM signals in patients with CHF have demonstrated acute haemodynamic effects and suggested improved quality of life and ventricular function.[2] More recent randomized studies have provided more objective evidence of safety and beneficial impact on exercise tolerance and quality of life.[5–8] Other

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mechanistic studies have shown improvements in left ventricular (LV) function and reversal of the abnormal foetal gene programmes characteristic of CHF back to the normal adult programme.[9] However, the impact of CCM on long-term mortality has not been assessed.

The present study was a retrospective analysis of the long-term survival of patients treated with CCM therapy at our centre.

Methods

Patients

This retrospective study included 54 consecutive patients who underwent implantation of an Optimizer™ system (IMPULSE Dynamics, Orangeburg, NY, USA) between June 2003 and June 2010 at our referral centre. The baseline characteristics of the patient population, as shown in *Table 1*, were typical for patients with severe symptomatic CHF with systolic dysfunction. All patients were clinically in New York Heart Association (NYHA) class III or IV with severely impaired LV function [LV ejection fraction (LVEF 23 ± 6%)]. Patients able to exercise underwent a cardiopulmonary exercise test (CPX) before the implantation procedure; 16 (30%) patients in NYHA class IV were not able to perform a CPX. In these cases, the peak oxygen consumption (VO_2peak) was set to 3.5 mL/min/kg equivalent to 1 MET.[10] The overall VO_2peak was dramatically impaired with a mean level of 10.0 ± 4.8 mL/min/kg. Levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) were dramatically increased. This patient cohort had end-stage heart failure with limited therapy options.

Patients were required to be on an appropriate, stable medical regimen for heart failure, including (unless shown to be intolerant) a diuretic, an angiotensin-converting enzyme inhibitor and/or angiotensin-receptor blocker, and a beta-blocker.

Most patients were not eligible for cardiac resynchronization therapy (CRT) due to the lack of dyssynchrony and narrow QRS complexes. Some patients had a pre-existing cardiac resynchronization therapy plus defibrillator (CRT-D) system and failed to benefit from CRT.[11] All patients had stable sinus rhythm, no recent myocardial infarction or clinically significant angina at implantation.

Study design

The implanted Optimizer™ system consisted of an implanted pulse generator and three pacing leads (a standard right atrial lead and two active fixation leads inserted into the lower right ventricular outflow tract and mid-septally). Haemodynamic responses to acute CCM signal application were measured during the implantation procedure with a Millar catheter placed in the LV. dP/dt_{max} was used as an index of systolic function at baseline and in response to acute CCM signal application. The mean baseline value of dP/dt_{max} of 719 ± 176 mmHg/s confirmed impaired LV contractility. Based on animal data, an increase of at least 5% was required for implantation of the device. Correlations between acute dP/dt improvement and clinical outcome are still missing. So we do not know exactly if an increase of 5% dP/dt_{max} is reproducible and high enough. Several factors might influence the acute improvement of contractility as pain, excitement, or even noise in the room. In the mean, 2.3 placement manoeuvres were necessary to reach the target increase of 5% dP/dt_{max}. Thus, none of the consecutive procedures had to be omitted.

During the study period, two versions of the Optimizer™ were used. The first-generation device (Optimizer 2) had a fixed battery with a lifespan of 6–12 months, which necessitated changing of the device. However, the second-generation Optimizer™ (Optimizer 3), introduced after the first 10 patients, had a rechargeable battery. Once available, the first 10 patients were also upgraded to Optimizer 3.

Active CCM treatment was delivered for a minimum of seven 1-h periods spaced equally over the day. Depending on clinical therapeutic

Table 1 Demographic data of patients at the time of implantation

	n (%) or mean ± std
Age (years)	63 ± 10
Gender	
Male	49 (91%)
Female	5 (9%)
Weight (kg)	83.8 ± 16
Body mass index (kg/m^2)	28.0 ± 5.8
Creatinine (μmol/L)	125 ± 41
MDRD-GFR (mL/min)	60 ± 22
Diabetes mellitus type 2	27 (50%)
Diet or oral medication	11 (41%)
Insulin therapy	16 (59%)
Cardiac disease	
DCM	29 (54%)
CAD	25 (46%)
NYHA class III/IV	54 (100%)
LV ejection fraction (%)	23 ± 6
LVEDD (mm)	67 ± 8.4
QRS width (ms)	122 ± 24
NT-proBNP (ng/L)[a]	4967 ± 4059
BNP (ng/L)[b]	421 ± 311
Calculated NT-proBNP (ng/L)[c]	5194 ± 4393
Sinus rhythm	54 (100%)
VO_2 peak (mL/min/kg)	10.0 ± 4.8
Exercise intolerance (no CPX possible)	16 (30%)
Medication	
ACE inhibitors	45 (83%)
Full dose	32 (59%)
ARB	9 (17%)
Full dose	5 (9%)
Beta-blockers	51 (94%)
Full dose	31 (58%)
Diuretics	54 (100%)
Aldosteron atagonists	40 (74%)
Cordarex	19 (35%)
Digitoxin	25 (46%)
Oral anticoagulation	23 (43%)

MDRD-GFR, modification of diet in renal disease glomerular filtration rate; DCM, dilated cardiomyopathy; LVEDD, left ventricular end-diastolic diameter; ACE, angiotensin-converting enzyme; ARB, angiotensin Receptor Blocker.
[a]Roche NT-proBNP assay, used after 2005 ($n = 40$).
[b]Biosite Triage BNP assay, used until 2005 ($n = 14$).
[c]Calculation of NT-proBNP from BNP using the following correlation equation: NT-proBNP (mg/L) = 15.9 × BNP (mg/L) −1024 for BNP values >300 ng/L and NT-proBNP (mg/L) = 6.29 × BNP (mg/L) +100.8 for BNP values <300 ng/L.

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Table 2 (*A*) Haemodynamic measurements at implantation procedure and (*B*) clinical course of patients with cardiac contractility modulation therapy

	***n* (%) or median (95% CI)**
(A) Haemodynamic measurements at implantation procedure	
Baseline LV-d*P*/dt_{max} (mmHg/s)	725 (CI: 675–775)
Relative rise LV-ΔdP/dt_{max} (%)	11.4 (CI: 10.2–13.5)
Clinical course:	
Median duration of CCM therapy (days)	627 (CI: 505–750)
ICD (additional to CCM therapy)	
ICD prior to Optimizer™ implantation	42 (78%)
ICD upgrade after Optimizer™ implantation	5 (9%)
No ICD therapy	7 (13%)
CRT (additional to CCM therapy)	17 (31%)
CRT prior to Optimizer™ implantation	10 (19%)
CRT upgrade after Optimizer™ implantation	7 (13%)
Further intervention	
PCI	4 (7%)
CABG	1 (2%)
Stenting A. carotis	1 (2%)
System exchange from Optimizer 2 (not rechargeable) to Optimizer 3 (rechargeable) before the year 2005	10 (19%)
Complications:	
Lead fracture	1 (2%)
Lead dislodgement (2 leads RV, 4 leads RA)	6 (11%)
Optimizer pocket revision	2 (4%)
System infection	6 (11%)
Dead—3 patients	
Still alive—3 patients	
System explantation due to infection	5 (9%)
Atrial fibrillation (loss of therapy)	
Episodes	14 (26%)
Electrical cardioversion	13 (24%)
Atrial flutter ablation	2 (4%)
Ventricular arrhythmias	
ICD shocks	6 (11%)
Adequate	5 (9%)
Inadequate	1 (2%)
Ablation therapy	2 (4%)
(B) Outcome of patients with cardiac contractility modulation therapy	
Death	24 (44%)
Cardiovascular	19 (35%)
SCD	3 (6%)
Pump failure	16 (30%)
Non-cardiac death	5 (9%)
Cancer	5 (9%)
Progress heart failure	
With use of LVAD	3 (6%)
Dead	2
Still alive	1
With HTX	1 (2%)
Combined endpoint (death, LVAD, HTX)	26 (48%)
Kaplan–Meier analysis	
All-cause mortality	
Median survival (days)	992 (756–)
Annual mortality rate (%)	18 (11–24)
Cardiac mortality	
Median survival (days)	1059 (806–)
Annual mortality rate (%)	17 (8–23)
Combined endpoint (death, LVAD, HTX)	
Median survival (95% CI, days)	967 (693–)
Annual mortality rate (%)	19 (12–26)
Predicted survival	
HFSS[a]	
Median score (95% CI)	−8.17 (−8.32– −7.76)
Mean predicted 1-year mortality (95% CI,%)	28 (23–33)
Patients with:	
Low risk (HFSS > 8,1)	28 (52%)
Medium risk (HFSS 7.2 . . . 8.09)	17 (31%)
High risk (HFSS < 7.19)	8 (17%)
SHFM[b]	
Median score (95% CI)	
Predicted 1-year mortality (%)	1.44 (1.25–1.63)
Mean (95% CI)	18.4 (14.3–20.1)

[a]Heart Failure Survival Score.
[b]Seattle Heart Failure Model.

success and actual stage of heart failure, CCM treatment duration was individually extended to maximum 16 h daily. Currently, no data are available concerning the optimal duration of CCM stimulation. Based on animal data, at least 7 h per day are recommended. Nevertheless we do not know whether a clinically relevant improvement could be achieved with a longer period of CCM stimulation. Dose-finding studies are still missing.

For most patients, the follow-up visits were every 3 months at the implantable cardioverter defibrillator (ICD) and heart failure outpatient clinic of our hospital. At every visit, the Optimizer™ system and the ICD were checked for proper function by a cardiologist and a technician.

Clinical course

A complete set of information was available for all of our patients, allowing us to analyse all technical complications due to lead fracture as well as technical changes such as upgrade to CRT. Episodes of atrial fibrillation (AF) were registered because they cause a loss of CCM therapy.

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Table 3 Predictors of all-cause death in univariate and multivariate analyses using classical risk factors (A) and major risk factors of Seattle Heart Failure Model score (B)

Parameter	All-cause mortality				
	Univariate		Multivariate		
	HR (95% CI)	P	HR (95% CI)	P	
(A) Classical risk factors					
Gender (♀:♂)	0.22 (0.06–0.84)	0.026	0.11 (0.03–0.46)	0.026	
VO_2 peak (mL/min/kg)	0.92 (0.84–0.99)	0.048			
Serum creatinine (μmol/L)	1.013 (1.004–1.02)	0.006	1.014 (1.005–1.02)	0.003	
Diabetes mellitus type 2	2.71 (1.16–6.38)	0.022	2.9 (1.20–7.02)	0.018	
Serum sodium (mmol/L)	0.912 (0.83–1.0)	0.042	0.91 (0.84–1.0)	0.5	
(B) Major risk factors of SHFM-score					Hazard-Difference to SHFM (mean HR of SHFM[16])
Diuretic dose (mg/kg per day)	1.73 (1.17–2.54)	0.006	1.54 (1.02–2.34)	0.039	0.362 (SHFM: 1.178)
SBP,10 mmHg (for SBP < 160 mmHg)	0.87 (0.63 - 1.2)	0.41	0.84 (0.59–1.198)	0.34	-0.037 (SHFM: 0.877)
16-haemoglobin	1.17 (0.95–1.43)	0.136	1.13 (0.93–1.37)	0.23	−0.11 (SHFM: 1.124)
100/Ejection fraction	1.048 (0.69–1.59)	0.83	0.97 (0.611.54)	0.91	−0.06 (SHFM: 1.03)
100/Cholesterol (dL/mg)	2.31 (0.27–19.36)	0.44	2.75 (0.32–23.9)	0.35	0.544 (SHFM: 2.206)

HR, hazard ratio;95% CI, 95% confidence interval; SBP, systolic blood pressure.
P = Wald test.

Statistical methods

Correlation between B-type natriuretic peptide and N-terminalpro-B-type natriuretic peptide

Brain natriuretic peptides were determined to assess heart failure severity. Until 2005, BNP levels were measured using the Biosite Triage BNP immunochromatographic assay; thereafter, the Roche NT-proBNP electrochemiluminescent assay was used to measure NT-proBNP. For better comparison, the previously published correlation between these two assays was used to calculate NT-proBNP from measured BNP values (see *Table 1*).[12]

Kaplan–Meier analysis and event predictors

The primary study endpoints were the all-cause mortality and a combined endpoint of death, implantation of LV assist device (LVAD) or heart transplant. The secondary endpoint was the cardiac mortality. Survival was described using Kaplan–Meier analysis. Factors were proved as event predictors for all-cause death using univariate and multivariate analysis (Cox proportional hazard). The multivariate analysis was performed with the parameters, which showed significance in univariate analysis using the Akaike Information Criterion (AIC) and likelihood ratio test ($P < 0.05$). Interactions between the included covariables were checked. Proportional hazards were tested exerting Schoenfeld residuals.[13] The open-source software 'R' version 2.9.0 (R Foundation for Statistical Computing, Vienna, Austria) was applied for all statistical tests.

Prediction of survival

Two main models exist to predict the risk of death/urgent heart transplantation in heart failure. The first is the Heart Failure Survival Score (HFSS).[14,15] It relies mainly on VO_2peak and other clinical characteristics [presence of coronary artery disease (CAD), intraventricular conduction delay, LVEF, heart rate, Na^+-concentration, and mean arterial pressure]. Because these data were available in the patient records, the score could be calculated for each patient at the time of the original implant. The HFSS provides three different risk strata: high risk when HFSS <7.19 (35%, 1-year survival), medium risk when 7.20<HFSS<8.09 (60%, 1-year survival), and low risk when HFSS >8.10 (88%, 1-year survival). Each patient was assigned to a risk strata and the mean value of HFSS and 1-year survival were calculated.

A second, newer model is the Seattle Heart Failure Model (SHFM) score.[16,17] It is a well-validated scoring system that relies on a combination of the following clinical parameters: age, gender, NYHA class, LVEF, CAD, systolic blood pressure, medication, lab test of sodium, cholesterol, haemoglobin, lymphocytes, and uric acid. All these parameters were available in the patient records except for lymphocytes and uric acid, which were not determined in each case. The SHFM score was calculated for each patient at the time of the original

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Optimizer™ implantation. For missing values of lymphocytes the mean value of the overall population was taken. Regarding the uric acid the missing values were replaced by the upper normal range limit. The mean SHFM score of all patients was computed and compared with the actual survival observed in the study cohort. The hazard ratios of the five covariables, most contributing to the predictive power of the SHFM (Wald χ^2)[16] were calculated for the study data to find potential differences between the study cohort and the SHFM score.

Results

Clinical course

The median duration of CCM therapy (equivalent to mean follow-up period) was 21 (95% CI: 17–25) months (censored data 20 months). In all, 78% of the patients had a pre-existing implanted ICD before CCM application. The remaining patients refused to accept two devices and decided in favour of the Optimizer™ device that offers the possibility of reduced heart failure symptoms. In five (9%) patients, an upgrade from ICD to CRT-D was performed following Optimizer™ implantation. In some other cases no ICD was implanted due to severe concomitant diseases such as progressed cancer. This may be a factor contributing to deaths due to fatal arrhythmias (i.e. sudden cardiac death, SCD).

Cardiac resynchronization therapy was provided in addition to CCM in 16 (31%) patients. Ten of these patients were CRT non-responders who received additional CCM therapy. The remaining patients were upgraded to CRT due to heart failure progression obviously caused by a new left bundle branch abnormality or permanent right ventricular pacing. Further cardiac interventions such as percutaneous coronary intervention, coronary artery bypass grafting, or carotid stenting were necessary in only a few cases (see *Table 3* for details).

Complications of CCM therapy are listed in *Table 2A*. We had six cases of lead dislodgement (mainly the right atrial lead) and one lead fracture. The Optimizer™ pockets had to be revised due to haematoma in two patients. Device-related infections occurred in six (11%) patients. Most of these device-related infections started with signs of pocket skin necrosis with secondary bacterial infections. The rechargeable Optimizer™ device aggregate is bigger than a conventional CRTD- or ICD device. This device geometry might be associated with local skin necrosis especially in patients with cardiac cachexia and loss of subcutaneous soft tissue. *Table 2A* summarizes these and other adverse effects.

Atrial fibrillation is a common problem in CHF and leads to loss of CCM therapy delivery. No AF patients at enrollment have been included due to the fact that CCM is only feasible in sinus rhythm or atrial-paced candidates. Fourteen (26%) patients had episodes of AF and all these patients had at least one electrical cardioversion. In two (4%) patients atrial flutter ablation was performed. Complete loss of therapy due to AF did not occur in any of the patients. In most patients, conversion to sinus rhythm could be achieved. Periods of AF were short, because the loss of CCM signal delivery by the Optimizer™ system provided the means of early detecting and treatment of AF. In one patient with permanent AF the atrial spike of the continuously stimulating ICD could be programmed and used to trigger the CCM therapy.

Regarding ventricular arrhythmias, six (11%) patients received an ICD shock, most of which were adequate. One patient received an inadequate ICD shock. Electrophysiological ablation therapy was performed in two (4%) cases due to recurrent ventricular arrhythmia.

Clinical outcome

There were 19 cardiovascular and 5 non-cardiovascular deaths. An analysis of the cardiovascular deaths showed that three were obviously sudden and 16 deaths were classified as caused by pump failure. Three patients got an LVAD due to progressive heart failure. Two of these patients died a short time later. One patient is still alive, having survived 36 months with a functioning LVAD. One patient was eventually transplanted [Heart exchange (HTX)] after 301 days of CCM therapy and is still alive.

The Kaplan–Meier analysis for all-cause mortality is shown in *Figure 1*. For all-cause mortality the median survival time was calculated at 992 (95% CI: 756–) days equivalent to a median death rate of 18.4% (95% CI: 11–24%) per year. The Kaplan–Meier curve of a combined endpoint of death, LVAD or HTX is also plotted in *Figure 1* and shows only a slight difference to the all-cause mortality.

The tested classical predictors of deaths in Cox model univariate and multivariate analyses are shown in *Table 3A*. Due to the small sample size, only five different covariables were included according to the recommendations of Vittinghoff and McCulloch.[18] We found significant predictors of the all-cause mortality, such as gender, VO_2peak, serum creatinine, diabetes mellitus type 2, and serum sodium. The covariables that showed significance in the univariate analysis were applied in the multivariate analysis using AIC criterion and the likelihood ratio test. The VO_2peak was omitted due to failing significance (*Table 3A*). No interaction or non-proportional hazard was found for the included covariables.

Prediction of mortality by survival models

Predicted survival was calculated independently by the HFSS and SHFM models. The results are shown in *Table 2B*. The median SHFM score was 1.44 (95% CI: 1.25–1.63). The mean SHFM 1-year mortality was calculated by averaging the mortality of each patient and was computed to be 18.4% (95% CI: 14.3–20.1). Using the median SHFM score the predicted survival curve for the entire cohort was plotted and compared with the actually observed Kaplan–Meier curve (*Figure 1*). The curves are nearly identical in the first 2.5 years of follow-up.

A subgroup analysis of CCM patients with low vs. high predicted 1-year all-cause mortality using the SHFM score ($P < 0.01$, log-rank test) confirmed the accordance between the predicted and the real survival rates in *Figure 2* ($n = 27$ for both groups).

After a long follow-up period of >3 years, the difference between the Kaplan-–Meier curve and the SHFM (*Figure 1*) may not be justified by CCM, but by statistical/methodical reasons. There are four main causes to explain these differences. First, the case number is small after >3 years of follow-up period (nine CCM cases in observation left). Secondly, the patients in this study had more progressed heart failure than in the SHFM studies (NYHA class III–IV in this study vs. NYHA class II–III in SHFM studies). Therefore, the long-term survival may be different

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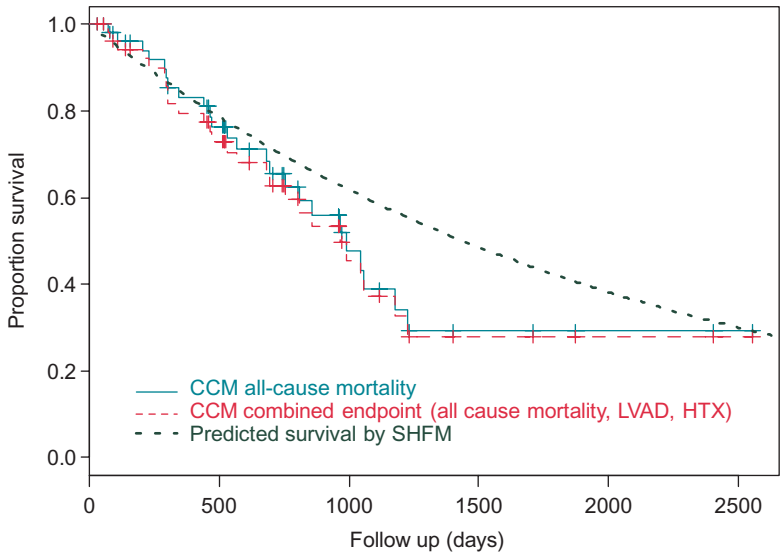

Figure 1 Kaplan–Meier analysis for the all-cause mortality and a combined endpoint including all-cause death, HTX, and left ventricular assist device ($n = 54$). Both curves are nearly identical. The all-cause mortality is compared with the survival predicted by the Seattle Heart Failure Model (dotted line) The cardiac contractility modulation survival rate is comparable with the predicted survival in the first 2.5 years.

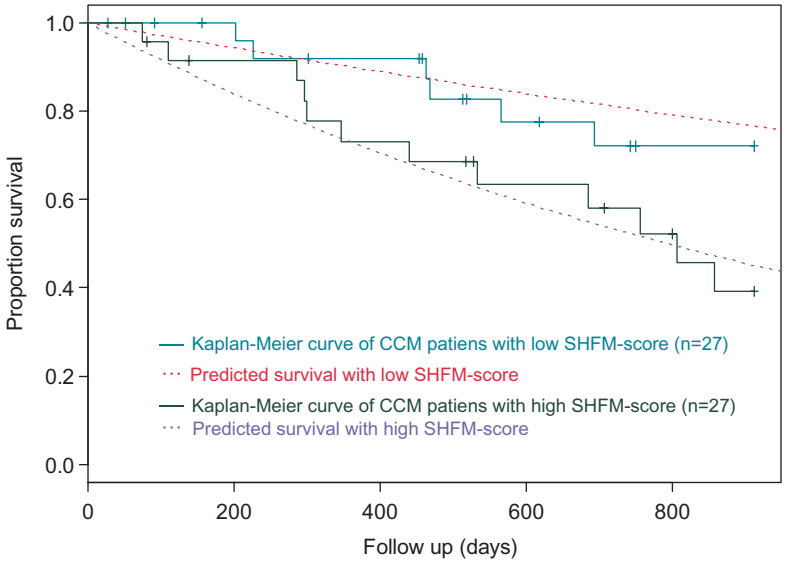

Figure 2 Strata of the all-cause mortality in patients with high (>1.45) and low (≤1.45) Seattle Heart Failure Model score treated with cardiac contractility modulation. The cut-off value was set to 16% (Seattle Heart Failure Model score of 1.45) aiming to get groups of identical size ($n = 27$). The log-rank test shows significant different survival ($P < 0.01$). The determined Kaplan–Meier curves are nearly identical to the survival predicted by the Seattle Heart Failure Model for both high and low Seattle Heart Failure Model scores. Due to the low case number the follow-up period was limited to 2.5 years (912 days).

after follow-up periods of >3 years. Thirdly, the proportion of diabetes mellitus type 2 was pretty high, ~ 50% in this study. Diabetes mellitus type 2 is not a considered covariable in the SHFM score. Cardiac contractility modulation patients with diabetes mellitus type 2 had dramatically poorer survival rate as predicted by SHFM score (*Figure 3A*). For the serum creatinine, which is also not included in the SHFM score, the deviation of the Kaplan–Meier curve and the SHFM are not so dramatically as for the diabetes mellitus type 2 (*Figure 3B*). Additionally, the fourth reason may caused by some missing values especially for lymphocytes in

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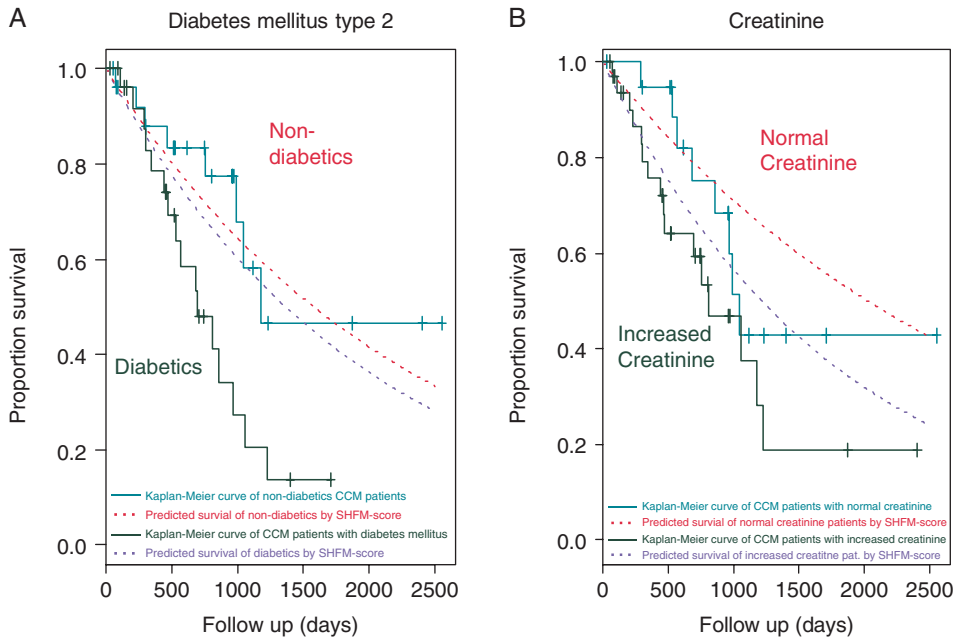

Figure 3 Strata of the all-cause mortality in cardiac contractility modulation patients with diabetes mellitus type 2 (*A*) and increased serum creatinine (*B*) compared with the Seattle Heart Failure Model score. Both parameters are not considered in the Seattle Heart Failure Model score. Especially cardiac contractility modulation patients with diabetes mellitus type 2 show dramatically poorer survival rate than predicted by Seattle Heart Failure Model score.

the study population, although it has to be mentioned that for initial development of the SHFM some missing lymphocyte values had to be replaced by averaged values from the first describing authors.[16] Due to these reasons, the divergence between the Kaplan–Meier curve and the SHFM can be ignored after >3 years of follow-up. Important is the concordance of the curves in the first 2.5 years follow-up.

For better comparison of the study population with the SHFM population the hazard ratios of the five most important covariables of the SHFM score were calculated for the study cohort. The results showed good concordance between the data of the study cohort and the SHFM score (*Table 3B*).

Discussion

A large number of patients have symptomatic heart failure despite all available treatments. Although CRT is a viable option for patients who also have dyssynchronous ventricular activation/contraction, only 50% of heart failure patients meet the criteria for implantation of a CRT device.[19] In addition, as many as 30% of patients receiving a CRT device are considered as 'non-responders'.[20] Thus, a treatment delivered by an implantable pulse generator through standard pacing leads that can provide similar clinical benefits in patients not presenting with asynchrony of the left ventricle could significantly enhance the therapeutic armamentarium for heart failure.

The results of existing studies showed the feasibility of delivering CCM treatment and demonstrated that left ventricular systolic performance could be acutely enhanced, as was shown in earlier pre-clinical studies.[1] Other studies showed these acute enhancements of the contractile state were not associated with changes in myocardial oxygen consumption.[9,21] Most recently, a multicentre, double-blind study (FIX4 study) provided additional confirmations of safety and efficacy with regard to exercise tolerance and quality of life.[6]

The present study represents the next early step in the clinical evaluation of CCM as a therapy for heart failure using long-term mortality as an endpoint of patient outcome. This is the first analysis to determine the long-term mortality in patients receiving CCM.

This was a single-centre, non-randomized retrospective analysis of patients implanted at our centre. Most implanted patients were functionally equivalent to HTX candidates, but had not qualified for HTX due to age or concomitant diseases. Cardiac contractility modulation was the last therapeutic option for these severely ill patients.

The clinical course showed good CCM tolerance. The most important side-effect was system infection, which was observed in 11% of the patients over the whole study period (~2% per year) and the necessity to exchange the first non-rechargeable generation device (Optimizer 2) after 6 months. System explantation is technically easy because all three screw-in leads were not heavily fibrosed and could be removed with very low risk.

Regarding all-cause mortality, the median survival time was 992 days with an annual death rate of 18% (95% CI: 11–24). The conclusion regarding survival benefit of CCM is difficult, because we

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had no control group in this study. There are several control groups from heart failure trials published in the literature. Depending on the inclusion criteria, the annual mortality rate shows huge variation between 7.5 and 75%.[22–23]

In our study, 30% of our patients were unable to perform CPX due to the severity of heart failure and therefore have to be judged as NYHA IV. In the COMPANION trial 18% were NYHA IV and in the CARE-HF trial only 7% were NYHA IV. [22,24] Our NT-proBNP level was nearly three-fold higher than in the CARE-HF.[24] Despite the obvious lower proportion of severe heart failure, the all-cause mortality of 19% in COMPANION is comparable with our CCM cohort.[22]

Instead of creating a small matched control group out of our patients we preferred an established and seriously published heart failure survival models to compare our data. There are mainly two different survival models in the literature. The older model is the HFSS. Determining the HFSS of the enrolled patients in our study, nearly half of the patients are at medium or high risk with a 1-year survival, <60%. A mean 1-year mortality of 28% could be predicted by the HFSS. This value is much higher than the real death rate of 18.4% per year determined in this study. The HFSS has attracted some criticism, because it may not be well validated and might deliver inaccurate results in patients on beta-blockers.[16]

The second newer survival model is the SHFM score. It is a well-validated score system using a combination of clinical parameters. Comparing the predicted survival by SHFM score and the real Kaplan–Meier analysis of our study, both plotted curves are graphically identical without any significant differences in the first 2.5 years (*Figure 1*).

A subgroup analysis was performed to identify subgroups that might experience greater benefit from the CCM therapy. Based on subgroup presentations of the still unpublished FIX-HF 5 Trial (personal communication) showing that patients with less impaired LV function might experience greater clinical benefit compared with end-stage heart failure without contractile reserve, patients were divided into two groups of high and low predicted 1-year survival based on the SHFM score (see *Figure 2*). It is interesting that also in these small subgroups the predicted survival of SHFM is nearly identical to the real observed Kaplan–Meier analysis.

Our data may suggest that there is at least no worsening of patient prognosis with CCM therapy. Cardiac contractility modulation seems to be a feasible and safe treatment option in many patients with no other therapeutic option. We also know from other studies such as the FIX-4 study that CCM therapy improves the symptoms of heart failure, physical working capacity, and quality of life.[6] We also observed this in a huge number of patients in our study. Our data might therefore support the theory that CCM is a clinically valuable symptomatic therapy if patient selection is based on end-stage heart failure as has been in the case in the past years.

Limitations

(1) This was a single-centre experience with a retrospective design and a limited number of patients. Because there was no randomized control group, our data had to be compared with existing heart failure survival models. For statistical/methodical reasons, the observation period had to be limited to 3 years of follow-up regarding the comparison between the survival rates of the study cohort and the SHFM score.

(2) Our experience has been derived from a very heterogenous group of patients as evidence by a mix of (i) patients with narrow QRS and patients with wide QRS who are documented CRT non-responders and (ii) inclusion of patients with predicted annual mortalities based on SHFM score ranging between 5 and 65% for individual patients.

(3) According to the safety features, the stimulation impulse of the therapy is currently limited to patients with sinus rhythm. Therefore, careful patient selection is necessary.

Conclusion

To our knowledge, these are the first data on long-term survival with CCM therapy in the literature. Cardiac contractility modulation seems to be a feasible and safe additional therapeutic option for patients with severe congestive heart failure. When compared with established heart failure scores, our long-term observational study demonstrate at least no worsening of survival in the treatment of patients with end-stage heart failure by CCM—partially as add-on to CRT—as has been done and as is customary in any new therapy. Our data should further encourage larger, randomized, long-term trials focusing on less severe heart failure patient and mortality as the primary endpoint.

Conflict of interest: none declared.

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