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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 ± 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 ± 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.

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

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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 ±