International Journal of Cardiology 277 (2019) 173–177

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiac contractility modulation treatment in patients with symptomatic heart failure despite optimal medical therapy and cardiac resynchronization therapy (CRT)

Jürgen Kuschyk [a,1], Herbert Nägele [b,1], Karl Heinz-Kuck [c,1], Christian Butter [d,1], Thomas Lawo [e,1], Dietmar Wietholt [f,1], Susanne Roeger [a,1], David Gutterman [g,*,1], Daniel Burkhoff [h,1], Benny Rousso [i,1], Martin Borggrefe [a,1]

[a] University Medical Centre, I. Medical Department, Mannheim, Germany
[b] Hospital Reinbek St. Adolf-Stift, Reinbek, Germany
[c] Asklepios Medical Center St. Georg, Hamburg, Germany
[d] Heart Center Brandenburg, Bernau, Germany
[e] University Hospital Bergmannsheil, Bochum, Germany
[f] Asklepios Klinik Wandsbek, Hamburg, Germany
[g] Medical College of Wisconsin, Milwaukee, WI, USA
[h] Columbia University, Cardiology, New York, USA
[i] Impulse Dynamics, Hod Hasharon, Israel

ARTICLE INFO

Article history:
Received 21 June 2018
Received in revised form 1 October 2018
Accepted 24 October 2018
Available online 29 October 2018

Keywords:
Cardiac contractility modulation
CRT
Non-responder
Heart failure
Exercise capacity
Quality of life

ABSTRACT

Background: A significant proportion of patients receiving CRT are non-responders. We evaluated the efficacy of Cardiac Contractility Modulation in subjects with reduced LVEF who, despite cardiac resynchronization therapy (CRT), continued to experience clinically significant symptoms.
Methods: This was a multi-center, open label, treatment-only, feasibility study of 17 CRT non-responders who received CCM therapy. Changes in NYHA class, ejection fraction (EF), Minnesota Living with Heart Failure Questionnaire (MLWHFQ) score, and exercise tolerance (6 minute walk test; 6MWT and peak VO_2) were analyzed over 6 months. Mortality and hospitalization rates were determined.
Results: Patients (82% male) were 69.4 ± 9.6 years of age with baseline EF = 22.8 ± 6.5%. Among primary endpoints, peak VO_2 increased 1.1 ± 1.6 ml/kg/min ($p = 0.03$) and MLWHFQ improved (−16 ± 16 points; $p < 0.01$). Mean NYHA class improved (−0.33 ± 0.49; $p = 0.02$), 6MWT increased (52 ± 60 m; $p < 0.01$), while EF trended up (2.9 ± 5.8%; $p = 0.08$) at 6 months. During the 6-month follow-up period, there were 18 hospitalizations in 9 subjects and 2 patients died.
Conclusions: Patients with heart failure and reduced ejection fraction who remain moderately to severely symptomatic despite use of CRT, may benefit from CCM therapy with improvement in quality of life and exercise tolerance. A larger prospective study in this population is warranted.

© 2018 Elsevier B.V. All rights reserved.

1. Introduction

Heart failure is a widely prevalent and growing health problem throughout the world. Development of therapies to improve heart function, relieve symptoms, reduce hospitalizations and improve survival is a high priority in cardiovascular medicine. Cardiac resynchronization therapy (CRT), when added to optimal medical therapy (OMT) in patients with symptomatic systolic heart failure, depressed left ventricular ejection fraction (LVEF), and prolonged QRS duration, improves heart failure symptoms, quality of life and exercise capacity and reduces hospitalizations and mortality [1,2]. Results from the recently published EchoCRT Trial demonstrate that patients with systolic heart failure and a QRS duration of <130 milliseconds (ms) not only failed to benefit from CRT, but also had potentially higher mortality [3]. Accordingly, the recently (2016) updated European Society of Cardiology (ESC) heart failure guidelines indicate a class I recommendation for CRT, only in patients with a QRS duration ≥130 ms and left bundle branch block (LBBB) pattern and a class II recommendation in patients with a QRS duration ≥130 ms and non-LBBB pattern [4]. Despite the careful selection criteria, approximately 30% of implanted patients fail to benefit

* Corresponding author at: Cardiovascular Center MEB, Medical College of Wisconsin, Milwaukee, WI 53226, USA.
E-mail address: dgutt@mcw.edu (D. Gutterman).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

https://doi.org/10.1016/j.ijcard.2018.10.086
0167-5273/© 2018 Elsevier B.V. All rights reserved.

from CRT highlighting the need for alternative device therapies in this population [5].

Cardiac contractility modulation (CCM) is an effective treatment for heart failure in patients who remain symptomatic on OMT and who have a narrow QRS duration. CCM has been recently referenced in the ESC HF guidelines [4] as a treatment which may be considered in patients with symptomatic heart failure and narrow QRS. It is not known whether CCM can serve as an effective treatment option in patients who fail to benefit from CRT.

CCM applies relatively high intensity, non-excitatory signals during the absolute refractory period of ventricular depolarization and has been shown to enhance the strength of left ventricular (LV) contraction and improve exercise tolerance and quality of life [6]. The mechanisms of action involve changes in myocardial gene expression, including a reversal of several components of the fetal gene program expressed in heart failure, and contractile protein phosphorylation and upregulation with improved calcium handling [6]. Three randomized trials have demonstrated that CCM improves heart failure symptoms, quality of life, and exercise capacity [7–10]. Since the mechanism of action differs from that of CRT, it may be expected that the effects of CCM are independent of and possibly additive to those of CRT and that CCM may be beneficial in patients where CRT does not improve symptoms of heart failure.

In fact, short-term studies have demonstrated that CCM can increase contractile force on top of that observed with biventricular pacing [11]. Nägele et al. in 2008 [12] studied CCM as an adjunctive therapy in 16 CRT non-responders with severe heart failure (markedly reduced LVEF and New York Heart Association (NYHA) Class III or IV symptoms). Significant improvement in LV dP/dt was demonstrated at the time of device implantation. After a follow up period of 147 ± 80 days, LVEF increased and NYHA symptoms improved significantly. CCM as an adjunct for CRT non-responders appeared to be safe and feasible; however, mortality and event rates remained high in this very sick population [12,13]. In a preliminary study, Nägele et al. found that baseline peak VO_2 was a clear and significant differentiator between survivors and non-survivors, suggesting that a baseline peak VO_2 of 9 ml/kg/min or more, best predicted a benefit from CCM [13]. These provocative findings by Nägele et al. [13] were obtained from a single center and need to be confirmed in a prospective multicenter cohort of patients. They also need to be extended to consider broader endpoints including heart failure hospitalizations, 6MWT, and peak VO_2.

The objective of the current investigation was to evaluate the efficacy of CCM using the OPTIMIZER™ III System in subjects from multiple sites in Germany who have reduced left ventricular function and who, despite OMT and cardiac resynchronization therapy (CRT), continue to experience clinically significant symptoms (e.g. NYHA III). The hypothesis is that CCM therapy improves quality of life and exercise tolerance (primary endpoints) as well as LVEF, NYHA symptoms, and that CCM in these patients, and reduces hospitalizations (secondary endpoints).

2. Methods

2.1. Patient population

Seventeen (17) patients with heart failure and reduced LVEF previously treated with CRT and deemed "non-responders" were implanted with an Optimizer™ device (IMPULSE Dynamics, Orangeburg, NY, USA) for CCM therapy. CRT non-responders were defined as heart failure patients on optimal medical management who did not improve symptomatically (i.e. remained at FC III) despite 6 months of CRT therapy. Each site PI was responsible for final adjudication regarding which patients met criteria for CRT non-responders.

To be included in this study, subjects had to be at least 18 years of age; have an implanted CRT device (CRT-D or CRT-P) for at least 6 months; be taking appropriate stable medical therapy for chronic heart failure (diuretic, beta-blocker, and ACE-inhibitor/ARB); and have an LV ejection fraction of 35% or less with clinically significant symptomatic heart failure (e.g., NYHA Class III).

Exclusion criteria were presence of end-stage or transient heart failure; baseline peak VO_2 of <9 ml O_2/kg/min; inability to perform exercise testing; potentially reversible cause of heart failure; active ischemia; heart failure hospitalization with intravenous diuretics or inotropic support within two weeks prior to enrollment; recent myocardial infarction (MI); scheduled CABG or a PTCA procedure; persistent atrial fibrillation or flutter; significant ectopy; mechanical tricuspid or aortic valves; and prior heart transplant.

2.2. Study design

This was a multi-center, open label, treatment-only, feasibility study conducted between January 2008 and September 2012. Basic information regarding medical history, NYHA classification, and medications was obtained for each subject. Eligible subjects were informed of the relative risks and potential benefits of participating in the study and then asked to provide signed informed consent. All enrolled subjects were then evaluated by a locally administered and interpreted echocardiogram, a cardiopulmonary stress test, a 6-minute walk test, a heart failure questionnaire, and a 24-hour Holter monitor.

All subjects came to the hospital between two and four weeks after implantation and activation of the Optimizer pulse generator for interrogation to determine the number of sensed beats, RV lead impedances and the duration of CCM signal delivery. The patients' CRT-P/CRT-D device was also interrogated with special attention to ICD settings and history of arrhythmic events and therapies delivered. Both devices remained active throughout the study period.

Subjects returned to the hospital for follow-up at study weeks 12 and 24 (with ± 2 week windows). At each visit, the CCM device was interrogated to ensure proper functioning. The subjects' CRT-P/CRT-D device was also interrogated. An interim medical history, including NYHA classification and medications, physical examination, and Minnesota Living with Heart Failure Questionnaire (MLWHFQ), were obtained. At the concluding 24-week study visit, a cardiopulmonary stress test, 6-minute walk test, and echocardiogram were also performed. After 24 weeks, subjects were asked to return for clinical follow-up visits according to the routine standard of the hospital. The study was conducted in compliance with the protocol, the Declaration of Helsinki, and was approved by the local Ethics Committees of each enrolling site.

2.3. Endpoints

The co-primary efficacy endpoints were mean change in quality of life, as assessed by the MLWHFQ, and mean change in exercise tolerance, as measured by peak oxygen consumption (peak VO_2) determined during cardiopulmonary exercise stress testing (CPX) at baseline and 24 weeks. The co-secondary efficacy endpoints included mean change in exercise tolerance, as measured by 6-minute walk test, mean change in left ventricular function, as assessed by echocardiographically determined EF, and mean change in heart failure class, as assessed by the NYHA classification. Other endpoints included the incidence of mortality, hospitalizations for any cause, and hospitalizations for heart failure. An interim analysis was made at 12 weeks for NYHA, 6MWT, and MLWHFQ. Safety outcomes including adverse events (AE) and serious adverse events (SAE) were also monitored and reported by each site.

2.4. Device and implantation

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 Optimizer was successfully implanted under local anesthesia and conscious sedation as described previously [5,6]. Briefly, intravascular access was achieved via the subclavian or cephalic vein after a right pectoral skin incision. Two screw-in leads (St Jude Medical Tendril) were placed under fluoroscopic guidance into the right ventricular septum and a third lead was fixed into the right atrium. Stimulus induced elevations in LV dP/dt_{max} (measured by Millar catheter) were used to establish optimal septal electrode placement so that CCM-induced increase in dP/dt_{max} of at least 5% was observed. After device implantation a cross-talk test was performed to exclude interference with the CRT-D device. CCM signals were delivered for at least 7 h per day.

2.5. Statistics

This was a nonrandomized, open label, treatment-only study. Changes in efficacy parameters are compared between baseline, 3 and 6 months, and evaluated by repeated measures analysis of variance. The threshold for significance was considered when $p < 0.05$. All data are reported as mean ± SE.

This feasibility study was not powered to demonstrate statistical significance of efficacy or safety parameters. The study was intended to provide information that may be used for the design of a subsequent randomized study in the same target population.

3. Results

A total of 19 subjects from 4 sites were enrolled and implanted with an Optimizer IPG device between January 2008 and September 2012. Two patients were excluded due to baseline CPX testing results with peak VO_2 <9 ml O_2/kg/min, results which were not available until after device implantation. The baseline characteristics of the remaining 17 subjects are typical for patients with advanced symptomatic heart

Table 1
Baseline demographics. Values are presented as M ± SE.

Baseline characteristics	Value (N/%)
Age	69 ± 9.6 (17)
Male	14 (82%)
Female	3 (18%)
Cardiomyopathy – ischemic	6 (35%)
Cardiomyopathy – dilated	10 (59%)
Cardiomyopathy – other	1 (6%)
dP/dt_{max} at implant	13.3 ± 4.6 (14)
NYHA Score	2.9 ± 0.2
MLWHFQ	45 ± 18
6 minute walk (meters)	264 ± 102 (16)
Peak VO_2 (ml/kg/min)	11.5 ± 2.2
LVEF (%)	22.8 ± 6.5
LVEDD (mm)	71.4 ± 9.5
Beta-blocker	17 (100%)
ACE-I/ARB	15 (88%)
AT1/AT2	2 (12%)
Diuretic	17 (100%)
Antiarrhythmic	6 (35%)

failure with NYHA III (94%) or II (6%) symptoms (Table 1). Baseline LVEF was 22.8% ± 6.5%, peak VO_2 was 11.5 ± 2.2 ml O_2/kg/min, and quality of life was impaired (MLWHFQ 45 ± 18). All patients were in sinus rhythm at the time of implantation.

The follow up period for all endpoints was 6 months. There was improvement in the co-primary endpoint of MLWHFQ at both 3 (−11.6 ± 20.3 points; $p = 0.04$) and 6 (−15.9 ± 16.1; $p = 0.02$) months of CCM therapy compared to baseline (Fig. 1A). Therefore, CCM therapy induces sustained improvement in quality of life measures in patients who were not responding to CRT treatment.

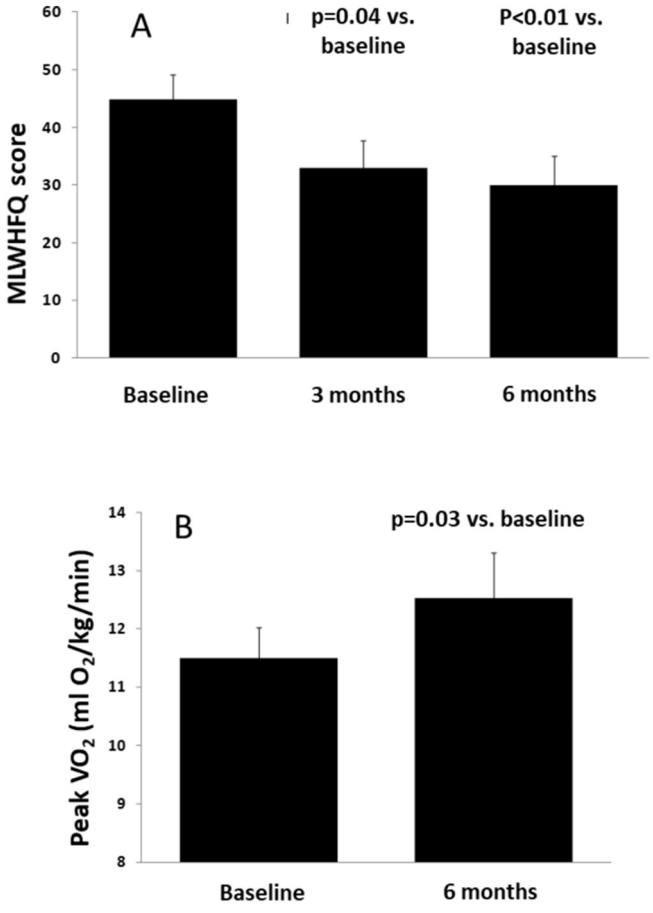

Fig. 1. Primary endpoints: A) MLWHFQ (mean ± standard error at baseline and 6 months); and B) peak VO_2 (mean ± standard error at baseline and 6 months).

The change in exercise tolerance, the other co-primary endpoint, measured by peak oxygen consumption (peak VO_2), was determined by cardiopulmonary exercise stress testing (CPX) at baseline and at 6 months follow up. The average peak VO_2 increased significantly after 6 months of CCM therapy compared to baseline by 1.1 ml/kg/min ± 1.6 ($p = 0.03$; Fig. 1B). Thus the beneficial effects of CCM in these subjects were sustained for at least 6 months, possibly due to structural improvement in heart failure [14].

Secondary efficacy endpoints of the study included exercise tolerance by 6-minute walk test, LVEF, and NYHA symptoms. Exercise tolerance as measured by 6-minute walk test improved with CCM therapy by 57 ± 84 m ($p = 0.02$) after 3 months of therapy and 52 ± 60 m ($p = 0.008$) after 6 months of CCM therapy compared to baseline (Fig. 2A). LVEF, as assessed by echocardiography at 6 months, showed a trend toward improvement (2.9 ± 5.8%; Fig. 2B, $p = 0.08$). NYHA class improved with CCM after 6 months (−0.33 ± 0.49; Fig. 2C, $p = 0.02$) with a trend to improvement after 3 months (−0.31 ± 0.60 vs. baseline, $p = 0.055$). These results indicate that CCM therapy can improve exercise tolerance, NYHA, and possibly ejection fraction in CRT non-responders.

A total of 19 adverse events (AEs) were reported in 9 patients during the study. Of these, 18 were serious adverse events (SAEs), reported in 9 subjects, including 2 deaths. One patient died from renal failure and one died from severe pneumonia; neither of which was classified by the investigator as related to the device or the procedure. Four (4) of the SAEs (in 3 patients) were reported to be associated with the procedure, and 4 of the SAEs (in 3 patients) were considered to be associated with the device (1 event in 1 patient due to diaphragm stimulation and 3 instances were observed in 2 patients of RA lead dislocation). Altogether, 6 SAEs in 5 patients were device or procedure related. Two (2) SAEs in 2 patients were HF or dyspnea related. There were 7 episodes of either atrial fibrillation or nonsustained VT in 4 subjects.

Event-free (composite of all cause hospitalization and mortality) survival curve throughout the follow-up period and up to one year is depicted in Fig. 3.

4. Discussion

The key findings from this multi-site feasibility study are that CCM is efficacious and safe in patients with moderate-to-severe heart failure on OMT, who do not respond to CRT. Following 3–6 months of CCM added to OMT and CRT, patients showed improvements in exercise tolerance (peak VO_2), and quality of life (MLWHFQ), as well as 6 minute walk distance, and NYHA classification, with a trend toward improvement in LVEF. These data highlight the potential for CCM as an effective therapy for patients (nearly one third) with heart failure in whom significant symptoms persist despite use of CRT.

Chronic heart failure is a major cause of hospitalizations and morbidity in developed countries. A large number of patients remain symptomatic despite optimal medical treatment [4]. CRT reduces morbidity and mortality in patients with chronic heart failure, severely reduced LVEF and wide QRS duration ms [1,2,15]. Evidence-based guidelines for treatment of heart failure published by the European Society of Cardiology indicate a class I recommendation for CRT, only in patients with a QRS duration ≥130 ms and left bundle branch block (LBBB) pattern or a class II recommendation in patients with a QRS duration ≥130 ms without LBBB [4]. However, only a fraction of the heart failure patients meet these criteria and as many as 30% of those treated with CRT are considered non-responders. Therefore, there is an unmet need for alternative or additional therapeutic options in this population.

The Optimizer device implanted in this study was shown to properly deliver CCM therapy in a safe and efficacious manner in the study population. The existence of two implantable devices, each with its own set of electrodes raises general questions about the number of leads required. However current experience with CCM combined with ICD or CRT devices has not identified a correspondingly larger number of complications. Future devices are likely to combine various features and

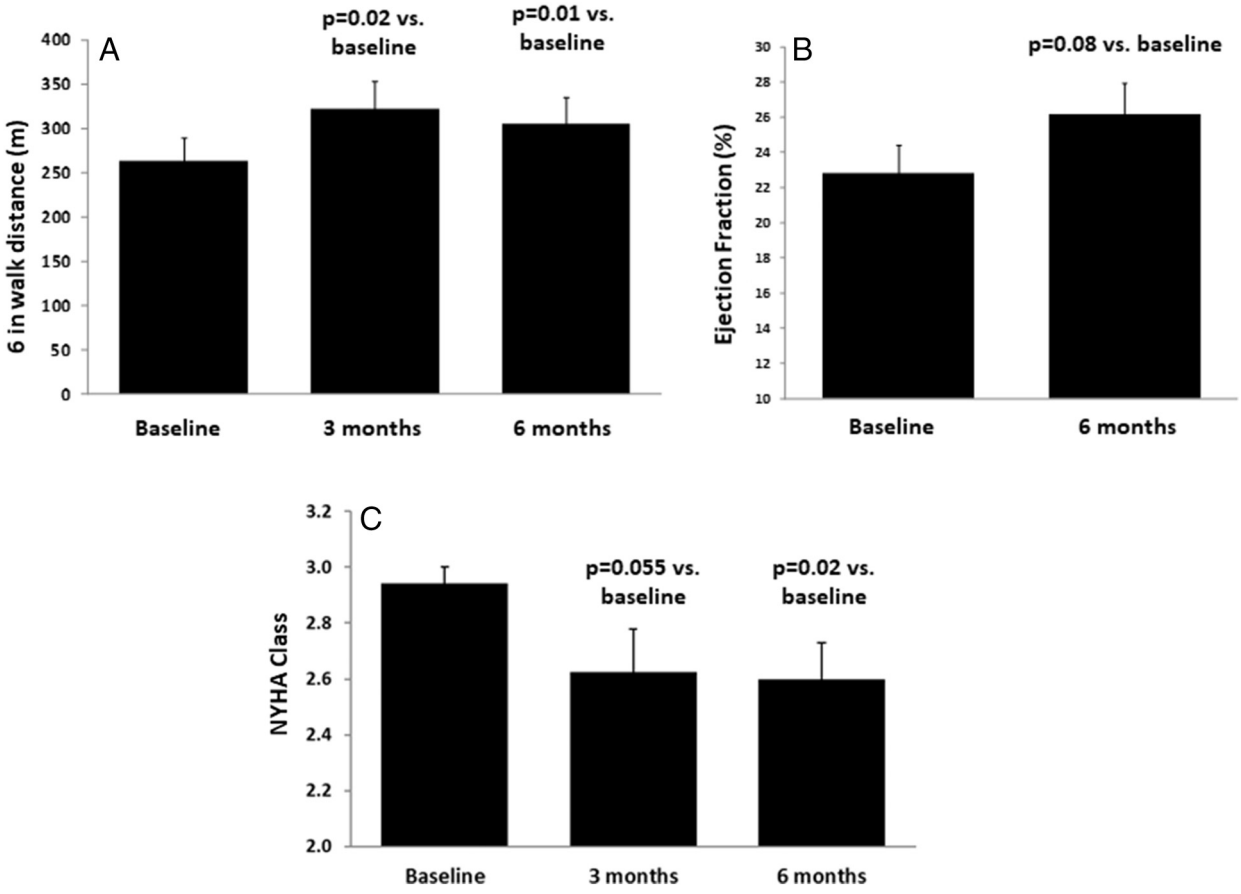

Fig. 2. Secondary endpoints: 6 minute walk distance (mean ± standard error at baseline, 3 and 6 months); left ventricular ejection fraction (mean ± standard error at baseline and 6 months); and NYHA classification (mean ± standard error at baseline, 3, and 6 months).

therapies thus reducing the number of implanted leads and size of the pulse generators. Currently used CCM delivery devices exclude the atrial lead, thus reducing the number of implanted leads from three to two.

All of the patients in our study had an active CRT-D at the time of the CCM system implantation. This is consistent with OMT in this patient population with very low LVEF. Although the numbers are small, our findings are consistent with a case report by Butter et al. and a case series reported by Nägele et al. [12,16] Both demonstrate that application of CCM in CRT non-responders is feasible, that safety hazards are not augmented, and that clinical improvements are observed.

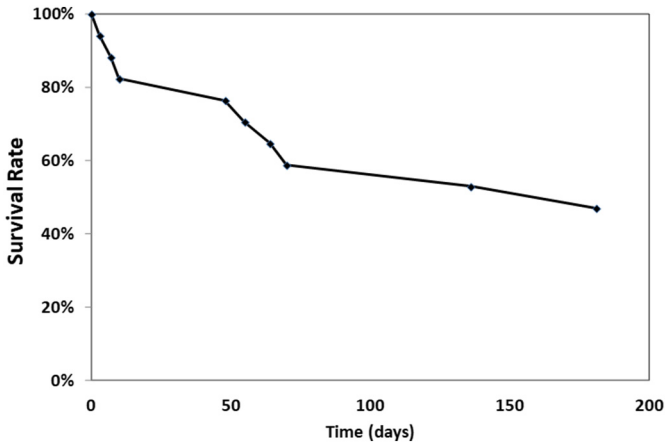

Fig. 3. Event-free survival (composite hospitalization and mortality of any cause).

The results of the present study are congruent with the findings of Nägele et al. [12], although the severity of symptoms at baseline was generally greater in the study by Nägele (higher MLWHFQ [61], NYHA [3.4]) and the EF was higher (22.8% in the present study and 27% in the paper by Nägele). Thus our findings extend the population of heart failure patients failing CRT who might benefit from CCM to include those with less severe symptoms. Furthermore, the data provide rationale for future studies of CCM in patients with wide QRS duration, a group that has previously been excluded from clinical trials of CCM. A specific, larger scale study looking at CCM in CRT non-responders is warranted.

5. Limitations

Several potential limitations should be mentioned. This was a small analysis without a randomized control group. Even with recruitment at 4 centers for up to 5 years only 19 patients were enrolled into the study. The reason for the unexpectedly low numbers of subjects is not known, especially given the relatively modest rate of CRT non-responders, but may represent difficulty in recruitment, subject reluctance to receive an additional implanted device, or other reasons. The key point is that among those who did receive CCM, a benefit was observed suggesting that the two interventional therapies are complementary and one may work when the other fails. A larger clinical trial is needed to determine the magnitude of the effect of CCM on heart failure in patients who fail CRT.

Changes in medication type and dose, e.g. addition of aldosterone-inhibitors or ivabradine were at the discretion of the treating physicians and might influence overall clinical status. However, drugs in these classes were not extensively used in this study.

For a number of outcomes, subjective assessment is necessary, opening up the possibility of a placebo effect with CCM, a confounding issue that is more prominent with implantable devices than traditionally observed with medications. For two reasons we believe this bias is minimal in our study. First, each patient has already failed a device inserted in a similar fashion. Thus our cohort may instead be a group predisposed to less of a placebo effect. Second, the FIX-HF-4 clinical trial was a double blinded cross-over trial that indicated that a placebo effect of CCM was observed at 3 months but this did not persist to the 6 month time point [8]. In the present study improvements at 6 months were similar or greater than those at 3 months, suggesting absence of a placebo effect.

The serious adverse event rate must be considered in relation to the acuity of the patients enrolled. The patients enrolled in this study had higher acuity of illness than typical heart failure populations since 1) by design they had class III symptoms despite medical therapy, and 2) they must also have failed CRT despite a clinical indication for this therapy. Thus the adverse event rate might be expected to be higher than in standard heart failure populations. Support for this explanation can be obtained by comparing with other study populations although caution is required since study durations and designs differ. For example in the largest randomized, controlled trial of CCM, FIX-CHF-5 [8], patients were younger (58 years vs 69 years in the current study); LVEF tended to be higher (26% vs 23% in the current study); LVEDD was smaller (63 mm vs 71 in the present study); and peak VO_2 was higher (14.7 vs. 11.5 in the present study) indicating lower acuity in FIX-CHF-5. The serious adverse event rate in in FIX-CHF-5 [8] (129 of 210 subjects) was 61% over a period of one year. In the present study 18 serious adverse events were recorded among 9 subjects (53%) over 6 months. Factoring in the longer follow-up time and lower acuity in FIX-CHF-5, one can speculate that the acuity- and time-adjusted serious adverse event rates are comparable between studies. Importantly most serious adverse events were not device-related. There were 6 serious adverse events in 4 subjects that were related to the procedure or device. A future longer study of CCM in CRT failure is needed to confirm this projection.

6. Conclusion

In patients with chronic heart failure who fail to benefit from CRT, treatment with Cardiac Contractility Modulation (CCM) may result in a significant improvement in function, quality of life, NYHA class, and peak VO_2 during intermediate follow-up without an increase in adverse events. This study supports a role for Cardiac Contractility Modulation as a safe and effective treatment for chronic heart failure patients with reduced left ventricular ejection fraction who fail to clinically respond to CRT.

Funding

Support for this study was provided by Impulse Dynamics, Orangeburg, NJ USA.

Potential conflicts of interest

Disclosure of potential conflicts of interest. The corresponding author (Jürgen Kuschyk), C Butter, and T Lawo have received modest speaker fees from IMPULSE Dynamics. D Burkhoff is a consultant to IMPULSE Dynamics. B Rousso is an employee of IMPULSE Dynamics. D Gutterman is a consultant for Impulse Dynamics and serves on their international advisory board. M Borggrefe and KH Kuck receive speaker's fees from Impulse Dynamics and serve on their International advisory board.

Research Involving Human Participants and informed consent. All subjects provided written informed consent. The institutional ethics boards approved the study prior to enrollment of any subjects.

References

[1] M.R. Bristow, L.A. Saxon, J. Boehmer, S. Krueger, D.A. Kass, T. De Marco, P. Carson, L. DiCarlo, D. DeMets, B.G. White, D.W. DeVries, A.M. Feldman, Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure, N. Engl. J. Med. 350 (2004) 2140–2150.

[2] J.G. Cleland, J.C. Daubert, E. Erdmann, N. Freemantle, D. Gras, L. Kappenberger, L. Tavazzi, The effect of cardiac resynchronization on morbidity and mortality in heart failure, N. Engl. J. Med. 352 (2005) 1539–1549.

[3] F. Ruschitzka, W.T. Abraham, J.P. Singh, J.J. Bax, J.S. Borer, J. Brugada, K. Dickstein, I. Ford, J. Gorcsan 3rd, D. Gras, H. Krum, P. Sogaard, J. Holzmeister, Echo CRTSG, Cardiac-resynchronization therapy in heart failure with a narrow QRS complex, N. Engl. J. Med. 369 (2013) 1395–1405.

[4] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, V. Falk, J.R. Gonzalez-Juanatey, V.P. Harjola, E.A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J.T. Parissis, B. Pieske, J.P. Riley, G.M. Rosano, L.M. Ruilope, F. Ruschitzka, F.H. Rutten, P. van der Meer, Authors/Task Force M, Document R, 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 18 (8) (2016) 891–975.

[5] E. Diaz-Infante, L. Mont, J. Leal, I. Garcia-Bolao, I. Fernandez-Lozano, A. Hernandez-Madrid, N. Perez-Castellano, M. Sitges, R. Pavon-Jimenez, J. Barba, M.A. Cavero, J.L. Moya, L. Perez-Isla, J. Brugada, Investigators S, Predictors of lack of response to resynchronization therapy, Am. J. Cardiol. 95 (2005) 1436–1440.

[6] M. Borggrefe, D. Burkhoff, Clinical effects of cardiac contractility modulation (CCM) as a treatment for chronic heart failure, Eur. J. Heart Fail. 14 (2012) 703–712.

[7] M.M. Borggrefe, T. Lawo, C. Butter, H. Schmidinger, M. Lunati, B. Pieske, A.R. Misier, A. Curnis, D. Bocker, A. Remppis, J. Kautzner, M. Stuhlinger, C. Leclerq, M. Taborsky, M. Frigerio, M. Parides, D. Burkhoff, G. Hindricks, Randomized, double blind study of non-excitatory, cardiac contractility modulation electrical impulses for symptomatic heart failure, Eur. Heart J. 29 (2008) 1019–1028.

[8] A. Kadish, K. Nademanee, K. Volosin, S. Krueger, S. Neelagaru, N. Raval, O. Obel, S. Weiner, M. Wish, P. Carson, K. Ellenbogen, R. Bourge, M. Parides, R.P. Chiacchierini, R. Goldsmith, S. Goldstein, Y. Mika, D. Burkhoff, W.T. Abraham, A randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure, Am. Heart J. 161 (2011) 329–337 e1–2.

[9] W.T. Abraham, K. Nademanee, K. Volosin, S. Krueger, S. Neelagaru, N. Raval, O. Obel, S. Weiner, M. Wish, P. Carson, K. Ellenbogen, R. Bourge, M. Parides, R.P. Chiacchierini, R. Goldsmith, S. Goldstein, Y. Mika, D. Burkhoff, A. Kadish, Investigators F-H- and Coordinators, Subgroup analysis of a randomized controlled trial evaluating the safety and efficacy of cardiac contractility modulation in advanced heart failure, J. Card. Fail. 17 (2011) 710–717.

[10] W.T. Abraham, K.H. Kuck, R.L. Goldsmith, J. Lindenfeld, V.Y. Reddy, P.E. Carson, D.L. Mann, B. Saville, H. Parise, R.C. Chan, P. Weign, J.L. Hastings, A.J. Kaplan, F.T. Edelmann, L. Luthje, R. Kahwash, G.F. Tomassoni, D.D. Gutterman, A. Stagg, D. Burkhoff, G. Hasenfuss, A randomized controlled trial to evaluate the safety and efficacy of cardiac contractility modulation in patients with moderately reduced left ventricular ejection fraction and QRS <130 ms, J. Am. Coll. Cardiol. Heart Fail. 6 (10) (2018) 874–883.

[11] C. Pappone, S. Rosanio, D. Burkhoff, Y. Mika, G. Vicedomini, G. Augello, I. Shemer, D. Prutchi, W. Haddad, R. Aviv, Y. Snir, I. Kronzon, O. Alfieri, S.A. Ben-Haim, Cardiac contractility modulation by electric currents applied during the refractory period in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy, Am. J. Cardiol. 90 (2002) 1307–1313.

[12] H. Nägele, S. Behrens, C. Eisermann, Cardiac contractility modulation in non-responders to cardiac resynchronization therapy, Europace 10 (2008) 1375–1380.

[13] H. Nägele, S. Behrens, I. Ollmann, C. Eisermann, Selection criteria of cardiac resynchronization non-responders (CRT-NR) for additional cardiac contractility modulation (CCM), ESC Heart Failure (HFA) Congress, 2009.

[14] C. Butter, S. Rastogi, H.H. Minden, J. Meyhofer, D. Burkhoff, H.N. Sabbah, Cardiac contractility modulation electrical signals improve myocardial gene expression in patients with heart failure, J. Am. Coll. Cardiol. 51 (2008) 1784–1789.

[15] W.T. Abraham, W.G. Fisher, A.L. Smith, D.B. DeLurgio, A.R. Leon, E. Loh, D.Z. Kocovic, M. Packer, A.L. Clavell, D.L. Hayes, M. Ellestad, R.J. Trupp, J. Underwood, F. Pickering, C. Truex, P. McAtee, J. Messenger, Cardiac resynchronization in chronic heart failure, N. Engl. J. Med. 346 (2002) 1845–1853.

[16] C. Butter, J. Meyhofer, M. Seifert, M. Neuss, H.H. Minden, First use of cardiac contractility modulation (CCM) in a patient failing CRT therapy: clinical and technical aspects of combined therapies, Eur. J. Heart Fail. 9 (2007) 955–958.