Cardiac Contractility Modulation Therapy for Heart Failure – First Romanian Experience
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ABSTRACT
Aim: The purpose of this study is to present the first Romanian case-series of patients with heart failure with reduced ejection fraction (HFrEF), supported with the newest generation of cardiac contractility modulation (CCM) device.

Methods and results: Sixteen patients (15 men), aged 66.6±7.49 years, were supported with OPTIMIZER® smart IPG CCMX10 device and followed-up for an average duration of 385.75±326.32 days. The etiology of HF was ischemic in 13 patients (81%), 8 patients (50%) had atrial fibrillation, mean creatinine clearance value was 55.8±13.87 ml/min, and 5 patients (31,2%) had diabetes mellitus. All patients were supported with an implanted cardioverter-defibrillator (ICD), while 5 patients (31.2%) had cardiac resynchronization therapy (CRT) on top. The pharmacological treatment has been optimized in all patients. Six months after implantation, the LVEF has increased from 25.93%±6.21 to 35.5%±4.31 (p=0.00002), NYHA class improved from 3.18±0.4 to 1.83±0.38 (p<0.0001), and exercise tolerance evaluated with 6-minute walking test (6MWT) increased (from 321.87±70.63m to 521.41±86.43m; p<0.00001). Three patients (18,7%) died during the follow-up period after 48, 108 and 545 days (one non-cardiac death).

Conclusions: Cardiac contractile therapy is a feasible, safe, and useful therapy for patients with HFrEF whose symptomatology is not improved with optimal standard therapy.

Keywords: heart failure; cardiac contractility modulation; cardiac devices; device implantation.

INTRODUCTION
Optimal treatment of heart failure (HF) includes, in addition to pharmacological treatment, implantable devices dedicated to correcting cardiac asynchronism and preventing sudden death1.

If ICDs had a favorably impact on sudden cardiac death2,3, devices dedicated for CRT still have notable deficiencies with a significant proportion of patients remaining symptomatic (about 30%, so-called „non-responders”4).

In addition, CRT is not suitable for about 70% of patients with HFrEF (patients with QRS ≤130 msec), meaning that most of these patients cannot be beneficiaries of this kind of non-pharmacological therapy5.
Here, CCM therapy comes to cover a remarkable gap. Unlike a pacemaker or a defibrillator, the CCM device is designed to modulate the strength of the cardiac muscle rather than the rhythm, and it is applicable for patients with HF with functional NYHA class II to IV, reduced or mid-range (up to 45%) LVEF, and low range of ventricular ectopic beats (less than 10,000 per day). The modulation of the myocytes' contraction strength is made by the generation of non-excitatory high voltage impulses (between 4.0V and 7.5 V according to patient’s tolerance, higher voltages being preferred). The stimulation train generally consists of two biphasic pulses having a total duration of 20.5–22.5 msec. Even though it is technically possible, the therapy is not required to be provided for 24 hours a day, thus it is provided at regular intervals throughout the day, for a total of 7 to 12 hours.

This novel device enhances cardiac contractility through a variety of processes\(^6\)–\(^8\). They primarily involve: (1) acute alterations in intracellular calcium handling, due to up-regulation of L-type calcium channels and to an improved calcium uptake into the sarcoplasmic reticulum, (2) chronic alterations in the expression and phosphorylation of important calcium regulators, and (3) the most important mechanism seems to be related with reversal of the fetal maladaptive myocyte gene program associated with HF and normalizes expression of key sarcoplasmic reticulum Ca\(^{2+}\) cycling and stretch response genes.

The device was first created and designed for patients with sinus rhythm (SR) with a narrow QRS, but it was later modified and adapted to be suitable for patients with atrial fibrillation (AF) as well as for non-responders to CRT (patients with a wider QRS).

The AIM of this paper is to present the evolution of the first series of patients in Romania who have benefited from the implant of a CCM device on top of the optimal standard pharmacological treatment, covering not only a proper medication, but also the recommended implantable devices (ICDs and CRT-Ds).

**METHOD**

Sixteen patients with clinically significant symptomatic HFrEF (e.g., NYHA Class III or IV) despite an appropriate therapy for chronic HF (diuretic, beta-blocker, and ACE-inhibitor/ARB and devices ICD or CRT-D), were supported with the latest generation CCM device—OPTIMIZER\(^\circ\) SMART IPG CCMX\(^10\) (Impulse Dynamics (USA) Inc. Orangeburg, NY, USA).

All the patients had an initial evaluation before the implantation procedure consisted in the assessment of the NYHA functional class, medication, and an echocardiographic evaluation of the heart (including cavities measurements, LVEF and left ventricle volumes, mitral regurgitation, and tricuspid regurgitation), acquired with a Vivid 7 machine (GE Healthcare). Blood samples for routine analysis were also taken. A six-minute walk test (6MWT) was performed at the baseline and at least once during the 6-month follow-up assessments. The devices already implanted (implantable cardioverter-defibrillators (ICDs) or cardiac-resynchronization and defibrillators CRT-Ds) were interrogated. Other potential uncorrected causes of HF (e.g., treatable coronary lesions and frequent ventricular ectopy) were evaluated before the implant.

The details related to CCM device implantation were described elsewhere\(^9\).

Active CCM treatment was programmed to be delivered daily for at least 7 h, in equally spaced-out intervals throughout the day, with a voltage between 5 and 7.5 V, on one or two channels, according to the patient’s tolerability, and to aim for at least a 40% CCM therapy delivery.

The ECG aspect of the CCM delivery in a patient with sinus rhythm is depicted in Figure 1.

**Statistics:** Student’s t-test for matched pairs was used to determine whether differences in clinical and hemodynamic data were significant. The mean and standard deviation is used to express all data.

**RESULTS**

A total of 16 subjects were supported with an Optimizer IPG device between November 2018 and May 2021. The mean follow-up time was 385.75±326.3 (15-896) days. The baseline characteristics of the enrolled patients are depicted in Table 1.

The mean age was 66.5±7.49 year and 15 patients were male. The etiology of HF was ischemic in 13 patients (81%) and non-ischemic in 3 patients (19%). History of previous myocardial infarction was recorded in 7 patients (43.7%) and 11 patients have had revascularization therapy (aorto-coronary by-pass in 4 patients and percutaneous angioplasty with stent implantation in 8 patients). One patient had both therapies. One third of patients had diabetes mellitus (5 patients), and hypertension was present in 3 patients. All off the patients had chronic kidney disease (7 patients stage two and 9 patients stage three) with mean creatinine clearance of 55.8±13.87 ml/min. Half of the patients had history of atrial fibrillation (AF), and two of them were in AF at the moment of device implantation. Five
patients were previously provided with CRT-D, and all the rest had ICDs.

The medical treatment was optimized, beta-blockers and mineralocorticoids antagonists were administered to all patients, and renin-angiotensin inhibitors in 14 patients (87.5%).

Six months after implantation, the LVEF has increased from 25.93±6.21 to 35.5±4.31 (p=0.00002), NYHA class improved from 3.18±0.4 to 1.83±0.38 (p<0.01), and exercise tolerance evaluated with 6-minute walking test (6MWT) increased (from 321.87±70.63m to 521.41±86.43m; p<0.00001) (Table 2).

Three patients (18.7%) died during the follow-up period at 48, 108 and 545 days after the CCM implantation. The first patient died of a severe cardio-renal syndrome with decreasing renal function and severe hyponatremia, and the second died of a non-cardiac cause (angiocolitis with septic shock). The third patient developed severe hypothyroidism as a result of autoimmune thyroiditis, was treated with corticotherapy, became decompensated, and died of irreversible cardiac pulmonary edema due to late hospital presentation in the context of COVID-19 pandemia.

**DISCUSSIONS**

Despite breakthroughs in pharmaceutical and non-pharmacological therapy during the previous decades, HF treatment has remained challenging. Although device therapy has shown to be effective, a considerable number of patients with HF continue to be sympto-
increased exercise tolerance and quality of life, as well as fewer HF hospitalizations, as compared to patients who did not get CCM10-13.

Further trials supported the earlier findings, demonstrating that CCM improves peak oxygen consumption (VO2), 6MWT distance, and quality of life [as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ)], and symptoms (NYHA class). Clinical advantages were found to be greater in a group of persons with an LVEF of 35% to 45%14-15.

Two other studies suggested that patients with a LVEF of 25% to 45% percent benefit the most with CCM16,17, but more recent real-world trials revealing an even more dramatic effect in a subgroup of patients with an ejection fraction of 35 to 45 percent18.

CCM therapy was, for the first time, included in the European Society of Cardiology’s (ESC) 2016 guidelines for the diagnosis and treatment of acute and chronic heart failure being indicated for selected patients1.

Very recently, the long-term effects of cardiac contractility modulation delivered by the Optimizer Smart system were evaluated in a prospective registry (CCM-REG). The study included the highest number of patients (503) from 51 European centers, followed for the longest time (3 years), and spanning the widest range of LVEF. Many patients were having AF. Patients with atrial fibrillation (AF) and normal sinus rhythm were studied in three terciles of LVEF (25%, 26–34%, and >35%). Cardiac contractility modulation therapy was remarkably effective despite optimal treatment, and only one-third of these patients may benefit from CRT therapy.

In this field, CCM represents an emergent therapy whose efficacy and safety was first evaluated in a small number of clinical trials, with results suggesting

Figure 2. Chest X-ray in a patient supported with CRT-D (left side of the thorax) and CCM device (right side of the thorax).

Figure 3. ECG aspect of the CCM delivery in a patient supported with CRT-D (note the small pacing artifact before QRS due to biventricular pacing and the big pacing artifact on top of QRS due to CCM delivery).
increased functional status, quality of life, LVEF (even in those with LVEF <25%), and lowered heart failure hospitalization rates as compared to patients' past histories\(^\text{19}\). The therapy may also seem to have a positive impact on survival.

The delivery of CCM therapy to patients who are considered non-responders to CRT is an intriguing element. Concerns were raised regarding the efficient CCM impulses delivery in patients with particularly wide QRS interval, as well as regarding the number of leads inside the patient's heart. An older version of the CCM device—OPTIMIZER III (a three-lead model (one atrial and two ventricular leads))—was evaluated, showing that the association of these devices appears feasible, but with some calculated risks, primarily related to various complications (e.g., lead dislodgement and arrhythmias)\(^\text{20}\). Another trial showed that the peak VO\(_2\), as well as exercise tolerance rose, while the LVEF trended upwards, and quality of life (assessed with the Minnesota Living with Heart Failure Questionnaire) improved\(^\text{21}\).

One third of our patients were supported with a CRT-D device, having a large QRS interval. The CCM therapy has been associated with good results even in these patients. Figure 2 illustrates the chest X-ray, while Figure 3 illustrates the ECG in such a patient.

The CCM therapy was previously contraindicated for patients with chronic or long-standing persistent atrial fibrillation or flutter, but a new product version—the OPTIMIZER\(^\circ\) SMART IPG CCMX10 was developed, allowing the atrial sensor lead to be removed if desired. This arrangement lowers lead-related problems (e.g., dislodgement, perforation, cardiac injury, mechanical obstruction of the superior caval vein, fracture, and infection), shortens the surgery, and provides a therapeutic advantage. The new model allows CCM therapy delivery on patients with permanent atrial fibrillation, which formerly was considered a contraindication for the previous generation of OPTIMIZER\(^\circ\) devices. First experience in heart failure patients with reduced ejection fraction and permanent atrial fibrillation was published in 2014\(^\text{22}\).

One half of patients included in our series have had history of AF, two patients were in AF at the implantation as this condition was permanent. The rest of the patients experienced many episodes of paroxysmal AF during the follow-up period, with little influence on CCM therapy delivery. Figure 3 illustrates the ECG aspect of CCM delivery in a patient having AF.

Our small series of patients was very heterogenous and included patients with wide range of LVEF (between 15% and 35%), non-responders to CRT therapy, as well as patients with AF history. The results were in line with most published data in the field.

**LIMITATIONS**

We just presented a summary of our findings from a small group of patients who were followed for varying lengths of time. We recognize that the NYHA classification is a highly subjective assessment of HF, and that
the results of echocardiographic data may be distorted due to the lack of blinding.

CONCLUSIONS
Cardiac contract modulation therapy is a feasible and useful therapy for patients with heart failure whose symptomatology is not improved with optimal pharmacological and non-pharmacological therapy, or for those who are not suitable for it (patients with no indication of cardiac resynchronization). The implantation of a second device on patients who have already implanted an ICD or have a CRT device appears not to be associated with additional risks.

Compliance with ethics requirements:
The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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