Case report

First use of cardiac contractility modulation (CCM) in a patient failing CRT therapy: Clinical and technical aspects of combined therapies

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Abstract

Cardiac contractility modulating (CCM) signals delivered by the OPTIMIZER System are being investigated as a treatment for medically refractory heart failure. Previous chronic studies of CCM have excluded patients with prolonged QRS and a cardiac resynchronization therapy (CRT) device. However, symptoms persist in more than 25% of these CRT patients. CCM may offer a therapeutic option for these non-responders. Here we report the first use of CCM signals in a patient who did not respond to treatment with a CRT-D device. We show that the implantation is technically feasible, that the OPTIMIZER and CRT-D devices can coexist without interference and that acute haemodynamic and clinical improvements can be observed. The results suggest that systematic investigation of CCM treatment in CRT non-responders is warranted.

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1. Background

Cardiac contractility modulating (CCM) signals are electrical impulses delivered during the absolute cardiac refractory period that enhance myocardial strength [1,2]. In isolated cardiac muscle, acute CCM signal application increases the action potential plateau voltage and enhances calcium entry [3]. When applied to a region of intact heart in normal animals and in animals with experimentally induced heart failure, CCM signals also appear to acutely enhance global ventricular strength through local increases in muscle contractility and change in load in remote regions [4,5]. Studies in experimental heart failure, however, have revealed that when applied chronically, CCM signals normalize expression of many abnormally expressed genes [6,7] and also normalize phosphorylation of several abnormally phosphorylated proteins characteristic of the heart failure state [6]. The mechanism of these molecular effects, which are now believed to underlie the chronic clinical effects of CCM, remain to be elucidated.

When delivered chronically to patients with medically refractory heart failure, CCM signals improve quality of life and exercise tolerance [8]. Previous chronic studies of CCM have excluded patients with prolonged QRS and a cardiac resynchronization therapy (CRT) device. However, more than 25% of CRT patients do not respond to therapy. These patients have few therapeutic options [9]. It has been suggested that CCM signals may offer a possible treatment option in these patients. This report summarizes the clinical and technical aspects of the first reported case of adding CCM treatment in a patient who did not respond to CRT.

2. Methods and results

A 69 year old man with ischaemic cardiomyopathy underwent pacemaker implantation (VVI, Biotronik) in 2001 at another hospital. He was first evaluated at our institution in February 2006, when he presented with symptomatic heart failure and atrial fibrillation. He was loaded with amiodarone...
and successfully cardioverted approximately two weeks later. From that point onwards he remained in sinus rhythm with intrinsic A–V conduction without the need for RV pacing. Due to persistent NYHA Class IV symptoms, ejection fraction (EF) of 10%, intrinsic QRS duration of 150 ms and echocardiographic evaluation revealing an interventricular delay (PA-AO: 40 ms) as well as an intraventricular delay (TSI triplanar SD 91 ms), the device was upgraded to a CRT-D device (Medtronic Insync Maximo with Medtronic ATTAIN 4193 unipolar LV lead) in April 2006. Coronary angiography performed prior to CRT-D implantation, showed the previously documented chronic occlusion of the right coronary artery with no progression of disease in other arteries. During CRT-D treatment, QRS duration remained prolonged at 180 ms. Despite 8 months of CRT-D treatment, the patient remained in NYHA class IV, required nasal oxygen and had persistent peripheral oedema. Blood pressure was 81/57 mm Hg and the patient did not tolerate β-blockade. Blood tests revealed an elevated NT-proBNP level of 8063 pg/ml. EF remained at 15%, with an LV internal diastolic dimension of 74 mm, 2+ mitral and tricuspid regurgitation and an estimated PAP pressure of 60 mm Hg. Medication at this time included furosemide (100 mg/day iv), spironolactone (50 mg/day), digoxin (0.07 mg/day), amiodarone (200 mg/day) and ramipril (2.5 mg/day).

In view of these persistent symptoms, it was decided to implant an OPTIMIZER System (IMPULSE Dynamics, Orangeburg NY) to deliver CCM signals, in addition to the CRT-D device. One atrial and two right ventricular septal pacing leads were inserted. A micromanometer pressure sensor (Millar Instruments, Huston) was advanced via the femoral artery into the LV to record responses to acute CCM signal application. The post-procedure chest X-ray shows the relative lead positions (Fig. 1). Following lead positioning, a relatively stable baseline haemodynamic state was established, followed by initiation of CCM signal delivery. \( \frac{dP}{dt_{\text{max}}} \) increased from a baseline value of 560 mm Hg/s (a normal reading being >1000 mm Hg/s) to 625 mm Hg/s within 10 min, representing an almost 12% increase (Fig. 2). Simultaneous tracings from the CRT-D and OPTIMIZER Systems are shown in Fig. 3 on two beats just prior to and just after initiating CCM signal delivery. The CCM signals are delivered within the QRS complex, and thus occur during the implantable cardioverter defibrillator (ICD) blanking period and are therefore not sensed by the ICD. After haemodynamic testing, additional testing of cross talk between the OPTIMIZER and the ICD was performed by varying the OPTIMIZER parameters over a broad range of settings, this demonstrated a lack of CCM signal sensing by the ICD and appropriate VF detection. The patient was discharged home the next day.

Six weeks after CCM implantation the patient had improved from NYHA class IV to II, LV end-diastolic dimensions decreased from 74 to 67 mm and ejection fraction increased from 15% to 20%. However, given the variability of echocardiographic assessment of ejection fraction, this change may not be clinically significant. Blood pressure had increased...
to 110/70 mm Hg and pulmonary systolic pressure had decreased from 60 to 46 mm Hg. NT-proBNP level decreased from 8063 to 4187 pg/ml.

3. Discussion

In a previous clinical study, it was shown that the acute haemodynamic effects of CRT and CCM signals are additive, when administered to patients with prolonged QRS duration and mechanical dyssynchrony [10]. This is because the mechanisms of these two types of therapy are different and unrelated [1]. However, prior studies of chronic CCM signal delivery have excluded patients already having a CRT device [10]. Since a relatively large proportion of patients receiving CRT have persistent symptoms and are considered non-responders [9], and because these patients have very few therapeutic options, it has been suggested that CCM signals might be a treatment option for such patients [10].

We report here the first use of the OPTIMIZER System in a CRT-D non-responder. From a technical standpoint, the OPTIMIZER System implantation procedure and device programming is not different to when the device is implanted in conjunction with a standard ICD. Formal testing at the time of implantation shows that the two devices can coexist without interfering with the proper functioning of the other. This was anticipated and is largely due to the fact that the CCM spike is delivered during the ICD blanking period.

The initial clinical response in this patient is encouraging. Increased EF, reduced end-diastolic dimension, decreased pulmonary pressures and decreased NT-proBNP levels are all consistent with the improvement in symptoms reported by the patient. Of course, prospective randomised trials are needed to evaluate the degree to which such effects can be reproduced in the challenging group of patients referred to as CRT non-responders.

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References


