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CASE REPORT
Heart failure

Cardiac contractility modulation as bailout in a patient with phospholamban p.Arg14del related cardiomyopathy intolerant to medication: a case report

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Background Cardiac contractility modulation (CCM) is a novel device-based therapeutic option in patients with heart failure with reduced ejection fraction who are not eligible for cardiac resynchronization therapy. Cardiac contractility modulation enhances cardiac contractility by delivering high-voltage non-excitatory electrical impulses during the absolute refractory period. Cardiac contractility modulation is known to improve left ventricular ejection fraction (LVEF), quality of life, and exercise capacity in heart failure (HF) patients.

Case summary We present a case of a 77-years-old woman with a cardiomyopathy associated with a pathogenic *PLN* variant [p.(Arg14del), Dutch founder mutation]. Due to progressive deterioration of LVEF (25%) despite maximally tolerated guideline-directed medical therapy (GDMT), a CCM device was implanted. After implantation, the patient experienced a sharp thoracic and interscapular pain after stimulation of one of the two leads. This lead was turned-off and the output on the other lead was increased to maximal output of 7,5 V. After 3 months, there were less signs and symptoms of HF. New York Heart Association class improved from class III to II and the patient was free of thoracic pain. Echocardiography demonstrated further improvement of LVEF to 44% and a decrease in end-diastolic pressures.

Discussion We describe a case of CCM therapy in a patient with HF related to a genetic cardiomyopathy due to a pathogenic variant in phospholamban *(PLN)*, persistent symptoms despite maximally tolerated GDMT. Although it was necessary to deactivate one of the both leads due to thoracic pain, LVEF and HF symptoms significantly improved. Further research is needed to elaborate on the potential role of CCM therapy in genetic cardiomyopathies.

Keywords Cardiac contractility modulation • Advanced heart failure • Genetic cardiomyopathy • Case report

ESC curriculum 6.1 Symptoms and signs of heart failure • 6.2 Heart failure with reduced ejection fraction • 6.5 Cardiomyopathy

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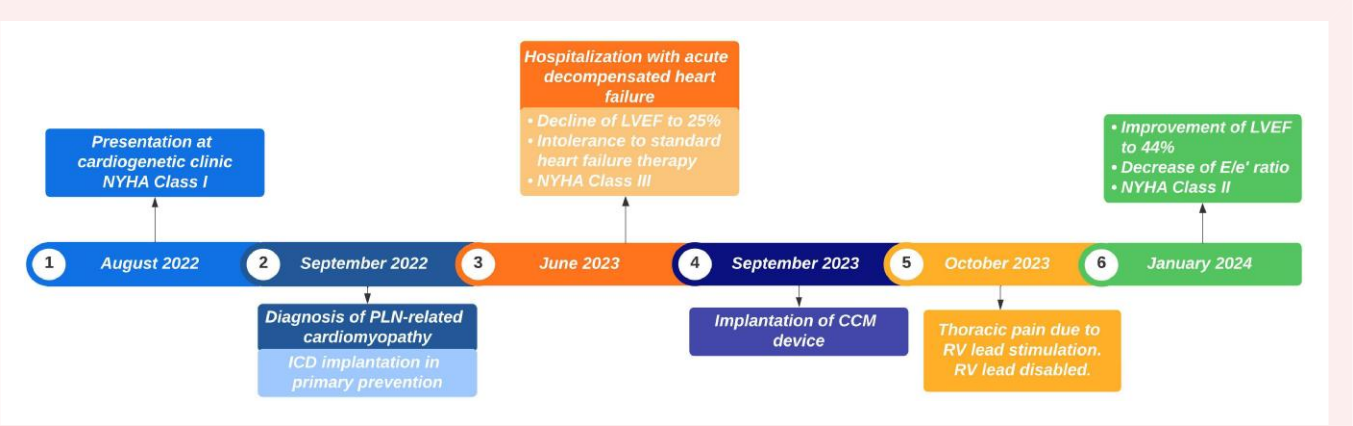
Learning points

- Cardiac contractility modulation (CCM) is a device-based therapeutic option that can improve functional status and left ventricular ejection fraction (LVEF) in patients with heart failure with reduced ejection fraction who are not candidates for cardiac resynchronization therapy (CRT) and remain symptomatic despite guideline-directed medical therapy.
- Extracardiac stimulation is a rare side effect of CCM and early recognition is essential.
- In our case, CCM proves to be a safe treatment option in patients with a pathogenic variant in phospholamban and improved LVEF and functional capacity despite the presence of cardiac fibrosis.

Introduction

Cardiac contractility modulation (CCM) is a novel therapeutic option in patients with heart failure (HF) with reduced ejection fraction, ineligible for cardiac resynchronization therapy (CRT). Cardiac contractility modulation is a device-based therapy that enhances cardiac contractility by delivering high-voltage non-excitatory electrical impulses during the absolute refractory period. Cardiac contractility modulation is known to improve left ventricular ejection fraction (LVEF), quality of life (QoL), and exercise capacity in HF patients.[1–3] The current ESC Guidelines on HF classify CCM as a device under evaluation, requiring further investigation in randomized controlled trials (RCT). It may be considered for patients with New York Heart Association (NYHA) class III–IV symptoms, and LVEF between 25% and 45%, and a QRS compex duration <130 ms.[4] We present a case of a 77-year-old woman with a cardiomyopathy due to the p.(Arg14del) pathogenic variant in the phospholamban (*PLN*) gene. Due to progressive deterioration of LVEF (25%) despite maximally tolerated guideline-directed medical therapy (GDMT), a CCM device was implanted.

Summary figure



Case presentation

A 77-year-old woman presented at the cardiogenetic clinic because of a positive family history of cardiomyopathy associated with a pathogenic *PLN* variant [p.(Arg14del), Dutch founder mutation]. Her past medical history included Parkinson's disease and cervical herniation. She reported no signs or symptoms of HF at initial presentation (NYHA Class I). Throughout the preceding year, she experienced two prodromal syncopes attributed to autonomic dysfunction because of Parkinson's disease.

The electrocardiogram displayed a normal sinus rhythm at 77 beats per minute, QRS width of 74 ms, P-wave enlargement, extremely low-QRS voltage without R wave progression and negative T-waves in the left precordial leads V4–V6 and inferior leads (Supplementary material online, *figure S1*). Echocardiography showed a preserved LVEF (56%), impaired global longitudinal strain (−15%), mild dilatation of left and right atrium, and a dilated hypocontractile right ventricle (RV; fractional area change 23%, basal RV diameter 4.8 cm, and mid-RV diameter 3.9 cm). At further work-up, cardiac magnetic resonance imaging revealed biventricular involvement: mild impaired left ventricular systolic function [ejection fraction (EF) 42%], dilatation of the RV with reduced EF (RV end-diastolic volume index 112 mL/m^2; RV ejection fraction 33%). Late gadolinium enhancement was extensively present mid-wall at the septal region and subepicardial at the mid to apical lateral region as well as diffuse interstitial fibrosis observed with T1 mapping (*Figure 1*). Coronary angiography demonstrated no significant coronary artery disease. Holter monitoring for 24 h showed a burden of ectopic beats of 2% (2087 single premature ventricular contractions and 37 couplets).

Genetic testing returned positive for the p.(Arg14del) *PLN* mutation. Bisoprolol 2.5 mg once daily was commenced. However, its administration was discontinued shortly thereafter due to symptomatic orthostatic hypotension. *PLN* is recognized as a high-risk genotype for sudden cardiac death (SCD). According to the *PLN* risk calculator, the patient had an 18.6% 5-year risk on malignant ventricular arrhythmias.[5] In shared-decision making, an implantable cardioverter-defibrillator was implanted for primary prevention of SCD.[6]

One year later, the patient was admitted with acute decompensated HF requiring intravenous diuretics. Echocardiography revealed a decline in LVEF to 25% and progressive dilation of the RV and both atria. Functional capacity had regressed to NYHA Class III. Guideline-directed medical therapy was initiated with perindopril 2.5 mg and bisoprolol 1.25 mg once daily. Due to symptomatic orthostatic hypotension, it was not possible to uptitrate these drugs nor associate mineralocorticoid receptor antagonists or sodium-glucose cotransporter two inhibitors. IV ferric carboxymaltose was administered because of iron

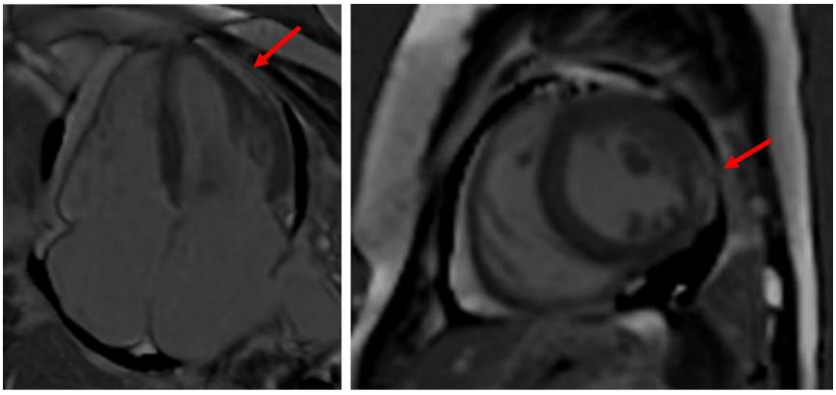


Figure 1 Cardiac magnetic resonance imaging showing a dilated cardiomyopathy with biventricular involvement; mildly reduced left ventricular EF (42%) and dilated right ventricle with reduced EF (33%). LGE phase-sensitive inversion recovery image of the four-chamber views and short-axis showing sub-epicardial LGE mid to apical anterolateral.

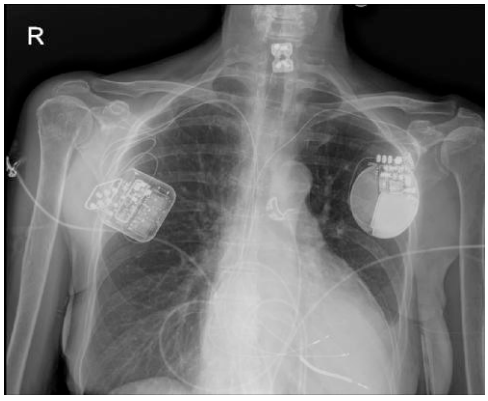


Figure 2 Chest radiograph after cardiac contractility modulation-implantation with two leads: local sense and right ventricular lead implanted in the right ventricular septum. The cardiac contractility modulation device is implanted at the right side and implantable cardioverter-defibrillator at the left side of the patient.

deficiency. After 2 months of maximally tolerated GDMT, LVEF had improved to 36% (*Video 1*); however, the patient experienced no improvement and remained in NYHA Class III.

Due to ongoing HF symptoms and signs despite receiving maximally tolerated HF therapy, the patient was deemed suitable for CCM implantation. After receiving patient's informed consent, a CCM device, Optimizer Smart (Impulse Dynamic) was implanted. Two leads, a RV lead and local sense (LS) lead were successfully inserted in the right ventricular septum *(Figure 2)*. No per-procedural complications were seen. The CCM device was programmed for 7 h daily therapy with output of 6 V on both leads. ECG after CCM implantation is shown in *the* Supplementary material online, *Figure S1*.

Two weeks after implantation, the patient presented at the emergency department with a sharp thoracic pain with irradiation to the interscapular region. No diaphragm stimulation was observed during clinical examination. A computed tomography scan showed no lead-related complications nor vascular, pericardial, or pulmonary pathology. Device interrogation revealed stable electric parameters. During device interrogation, the pain disappeared immediately after disabling the RV lead. Therefore, the RV lead was deactivated, and the output of the LS lead was increased to maximal output of 7.5 V with 10 h of daily therapy.

After 3 months, there were less signs and symptoms of HF. NYHA class improved to class II. Cardiac contractility modulation therapy was delivered in 99.1% of all eligible beats and the patient was free of thoracic pain. Echocardiography demonstrated a further improvement of LVEF to 44% and decrease in *E*/*e'* ratio (*Video 2*). Perindopril could be doubled to 2.5 mg twice daily, without eliciting symptomatic hypotension.

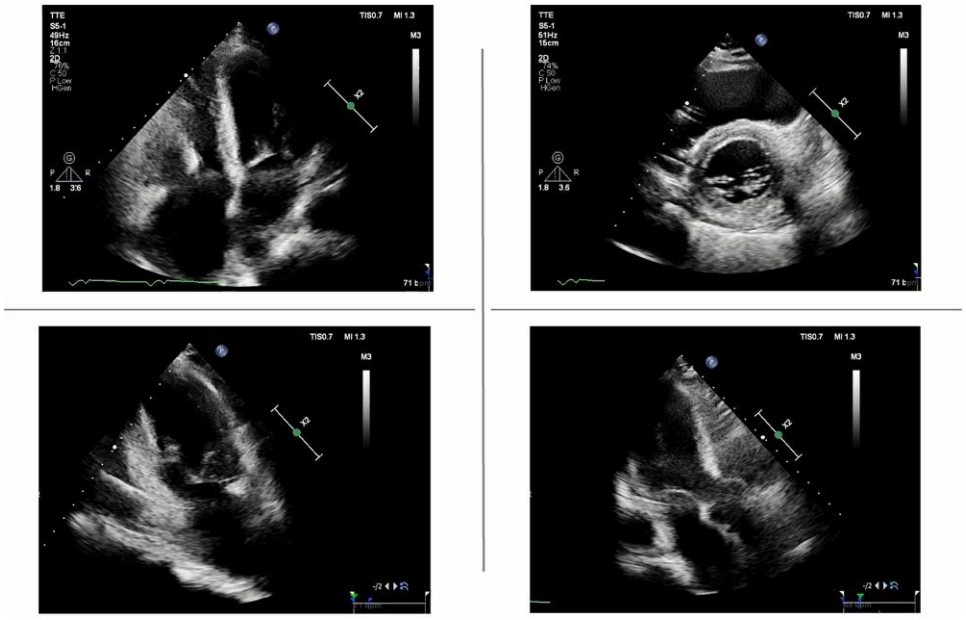
Discussion

We describe a case of a patient with a *PLN*-related cardiomyopathy treated with CCM. Cardiac contractility modulation therapy is a novel device therapy, which gives a non-excitatory high-voltage electrical signal during the refractory period. Randomized controlled trials prove a benefit of CCM on exercise capacity, QoL and LVEF.[1–3] Furthermore, findings from the CCM-REG, a real-world registry, demonstrate a decrease in mortality and HF hospitalizations over a 3-year follow-up in patients with EF ranging from 35% to 45%.[7] According to ESC Guidelines, CCM can be considered as adjunct treatment in patients with HF (LVEF between 25% and 45%) and refractory symptoms (NYHA III–IV) despite GDMT, who are not eligible for CRT.[4] Although case reports have suggested the potential role of CCM therapy in patients with dilated cardiomyopathy, its effects on specific genetic defects remain largely unknown.[8]

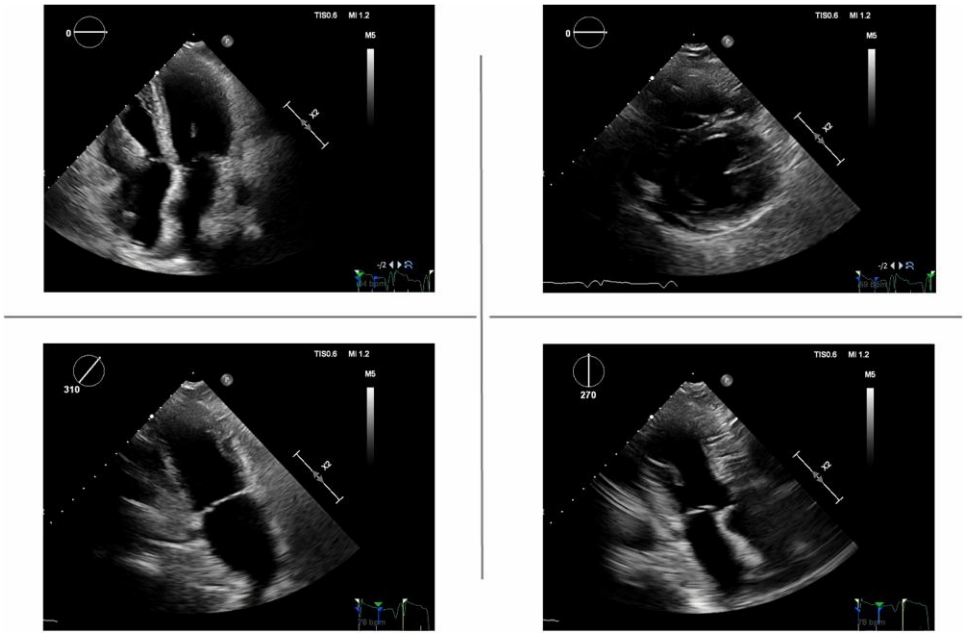
Phospholamban is a key regulator protein localized in the membrane of the sarcoplasmic reticulum that modulates Ca^{2+} homeostasis through reversible inhibition of SERCA2a.[9] Dephosphorylated PLN is an inhibitor of SERCA2a and phosphorylation by protein kinase A or calcium-calmodulin-dependent protein kinases (CAMKII) relieves these inhibitory effects. In dogs with HF, CCM therapy induced phosphorylation of PLN within 2 h of signal application.[10] Phosphorylation of PLN enhances intracellular calcium cycling capacity and, hence, contractility. In a substudy of FIX-HF-4, a double-blind, cross-over RCT,[1] CCM also increased gene expression of SERCA2a and *PLN*.[11] The p.(Arg14del) *PLN* pathogenic variant results in a gain of function of *PLN* with a chronic suppression of SERCA2a activity.[12] In addition,

patients have typical PLN protein aggregates, based on a poisoned gene product from the mutated allele. There is no specific treatment for p.(Arg14del) *PLN*-related cardiomyopathy, and this phenotype is often resistant to standard HF therapy.[13] In this case, CCM therapy proved to be safe in *PLN*-related cardiomyopathy and led to a modest improvement in LVEF.

Extracardiac stimulation due to CCM is a rare side effect. In a safety analysis of the FIX-HF-5 study, a prospective RCT comparing CCM to GDMT, only 2 of 215 patients experienced similar symptoms.[2] In our case, the RV lead was disabled. Nevertheless, a decrease in overall electrical stimulation does not necessarily imply a decrease in therapeutic effect. An RCT in 48 HF patients comparing the efficacy of CCM with one



Video 1. Echocardiography showing partial recuperation of left ventricular ejection fraction to 36% after 2 months of maximally tolerated dose of guideline-directed medical therapy.



Video 2. Partial recuperation of the left ventricular ejection fraction to 44% on echocardiography 3 months after cardiac contractility modulation-implantation.

vs. two intraventricular leads demonstrated comparable outcome in terms of improvement of NYHA class, QoL and peak oxygen uptake.[14]

In this case, LVEF improved even in the presence of extensive cardiac fibrosis, an early feature in *PLN* p.(Arg14del) variant carriers.[15] Prior experimental studies have demonstrated that CCM therapy has a beneficial impact on extracellular matrix composition, leading to a significant reduction in both interstitial and replacement fibrosis volume fractions.[10] However, this antifibrotic effect has not yet been thoroughly investigated or confirmed in humans. The reverse remodelling induced by CCM may be attributed to the normalization of mRNA and protein expression of cytoskeletal proteins, such as matrix metalloproteinases.[16]

Conclusion

We describe a case of CCM therapy in a patient with *PLN*-related cardiomyopathy, persistent symptoms, and intolerance to HF drugs. Despite the need to inactivate one of both leads due to thoracic pain, LVEF partially recuperated, symptoms improved, and GDMT could be increased. Further research is needed to elaborate on the potential role of CCM therapy in genetic cardiomyopathies.

Lead author biography

Faro Verelst is a resident specializing in cardiovascular disease at the University Hospital of Antwerp. Concurrently, she is pursuing her PhD, with a primary research focus on innovative device therapies for heart failure patients.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

Consent: The authors confirm that they obtained informed written consent for the submission and publication of this case report, including images and associated text, in accordance with COPE guidelines.

Conflict of interest: There are no conflicts of interest to declare.

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Data availability

The data underlying this article are available in the article.

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