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CASE REPORT

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# Cardiac resynchronization therapy with multipoint pacing in a patient with cancer therapeutics-related cardiac dysfunction

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**Abstract**

Cardiac resynchronization therapy (CRT) with multipoint pacing and quadripolar lead implantation showed improvement in systolic function, reduction in left ventricular volumes, and improved functional capacity in a patient with cancer therapeutics-related cardiac dysfunction; this therapy could be a valid option in those cases where a suboptimal CRT response is expected.

**KEYWORDS**

cancer therapeutics-related cardiac dysfunction, cardiac resynchronization therapy, multipoint pacing, non responders

## 1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) is one of the mainstays in the treatment of heart failure, as it has shown a reduction in mortality and morbidity and an improvement in functional capacity.[1] Yet not all those who receive this therapy do have an adequate response: 30%-40% of patients (so-called "nonresponders") do not show any improvement in hemodynamic parameters, reverse remodeling of the left ventricle, symptoms, and/or prognosis.[2,3] The causes of this lack of improvement are likely to be multiple and to be linked both to patient's clinical features (usually "nonresponders" are male, with postinfarction ischemic heart disease and with narrow QRS) and to device features.

The presented clinical case shows how some diagnostic tests carried out before the implant can provide useful information about the probability of the patient's response to CRT, and that the optimization of CRT, obtained using a new form of stimulation, multipoint pacing (MPP), with implantation of left ventricular quadripolar lead, is able to determine an improvement of hemodynamic and functional parameters.

## 2 | CASE HISTORY/EXAMINATION

A 70-year-old man with a history of arterial hypertension, chronic obstructive pulmonary disease (COPD), dyslipidemia, and mild chronic renal failure performed an echocardiogram, as requested by his reference oncologist, in October 2015. The patient was suffering from a non-small-cell lung cancer, diagnosed in 2005, already treated with multiple cycles of chemotherapy based on carboplatin, docetaxel, erlotinib, and radiotherapy. Surgery was contraindicated. Since 2011, malignancy was in phase of quiescence. In 2009, as part of a routine cardiology check, the patient was found to be affected by dilated cardiomyopathy with complete left bundle branch block. He had no family history of cardiomyopathies. The first echocardiogram carried out after this finding showed mild dilation of the left ventricle (left ventricular end-diastolic volume [LVEDV]: 170 mL, left ventricular end-diastolic diameter [LVEDD]: 62 mm), with presence of dyssynchronous interventricular septum movement, mild reduction in left ventricular systolic function (left ventricular ejection fraction [LVEF]: 45%), and mild mitral

regurgitation. The patient started the optimal medical therapy for heart failure and performed annual-basis follow-up.

Coronary angiography revealed the presence of nonobstructive coronary artery disease affecting the major epicardial vessels; a dobutamine stress echocardiogram was performed, with infusion protocol at both low and high doses, which demonstrated the absence of "contractile reserve" of the left ventricle without the appearance of ischemic changes.

## 2.1 | Investigations and treatment

In October 2015, the patient complained of worsening dyspnea with progressive reduction in tolerance to even slight physical efforts (NYHA class III). The medical therapy under way was as follows: carvedilol 12.5 mg bid, enalapril 5 mg bid, and spironolactone 50 mg od.

The echocardiogram performed at our clinics showed a "severely dilated left ventricle with severely depressed global systolic function (LVEF: 20%). Intraventricular and interventricular dyssynchrony [...] Mitral valve: symmetric tethering of the leaflets with moderate-to-severe regurgitation. Tricuspid: moderate-to-severe regurgitation [...]."

A cardiac magnetic resonance imaging (cMRI), performed in November 2015, confirmed morphological, functional, and flow data established by echocardiogram (Video S1); left intraventricular dyssynchrony was evident, evaluated through volume/time left ventricular curve and its derivative (Figure 1), with a delayed activation pattern of the lateral wall with respect to the interventricular septum; moreover, areas of subepicardial hyperenhancement at the basal level of the inferior, anterior, and anterolateral walls, with a nonischemic pattern (Figure 2), were reported in the sequences acquired late after administration of gadolinium (breath-hold contrast-enhanced T1-weighted inversion recovery gradient echo sequences to detect late gadolinium enhancement).

Following these evaluations, the patient was referred to a cardiac resynchronization therapy and defibrillator (CRT-D) implantation. The implant was effectively performed in November 2015 (QUADRA ASSURA CRT-D; Abbott Cardiovascular). In this circumstance, a quadripolar left ventricular lead was implanted in an inferior-lateral vein (QUARTET; Abbott Cardiovascular).

Immediately after implantation, it was decided to activate the MPP stimulation modality, with automatic optimization of the device stimulation algorithms (stimulation of two points of the left ventricle—from the most distal and the most proximal electrodes—at a very short temporal distance, 5 ms, and subsequent stimulation of the right ventricle, after 30 ms). This configuration showed a good result in terms of both the threshold values and the morphology of the ECG; there was also no stimulation of the phrenic nerve. The patient was discharged on the third day after implantation without complications and with the same medical therapy for heart failure as before admission.

## 2.2 | Outcomes and follow-up

The interrogations of the device, performed respectively in January 2016 and in January 2017, showed optimal parameters (biventricular pacing > 99%, atrial pacing < 1%, atrial fibrillation detected: 0%, no tachyarrhythmia detected) and stimulation thresholds; the ECG showed a QRS of good morphology (absence of notching in the QRS in the precordial leads, presence of R wave in V1; Figure 3) and of reduced duration compared to baseline (from 160 ms at baseline to 150 ms); the echocardiogram showed a moderate recovery of the global systolic function (LVEF: from 20% to 28%); there was a marked reduction in the degree of mitral and tricuspid regurgitation (from moderate-to-severe to mild-to-moderate) and a reduction in the LVEDV (from 247 to 197 mL) and in the LVEDD (from 75 to 69 mm) (view Figure 4 and Video S2).

The patient also showed an improvement of functional capacity (NYHA class II). Unfortunately, after 2 years the patient had an unexpected tumor recurrence and he died of a malignancy-related complication (cerebral thromboembolism).

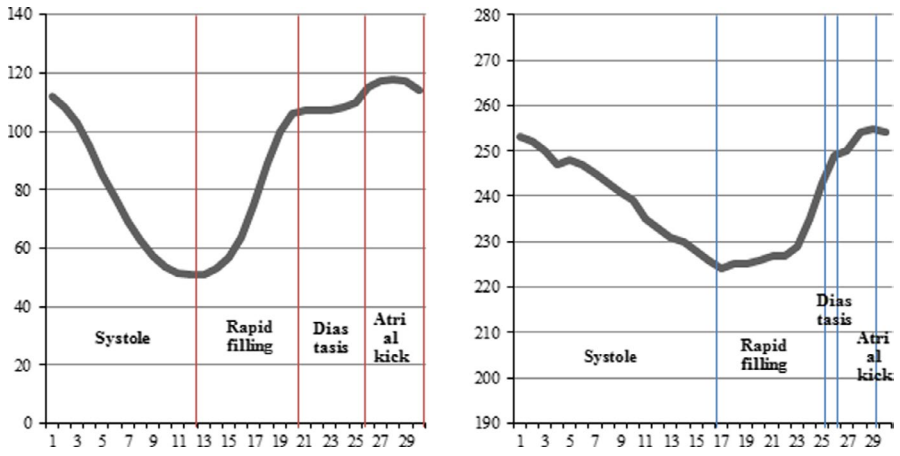


**FIGURE 1** Volume/time left ventricular curve in a healthy control (on the left) and in the patient of the case (on the right). One can notice the dissynchrony of the left ventricle, in the case patient, which renders both systole and diastole less effective than those of the healthy control. On the abscissas: the phases of the cardiac cycle. On the ordinates: the volume of the left ventricle

## 3 | DISCUSSION

The peculiarity of this clinical case lies in the reasoned use of the diagnostic and therapeutic tools available, both to evaluate the probability of response to CRT and to improve the functioning of the device.

The probability of CRT response can be estimated on the basis of some basic clinical data[4]; in the case of our patient, left bundle branch morphology of the QRS and the nonischemic etiology of cardiomyopathy suggested for a good probability of response; instead, male sex and, indirectly, the high degree of left ventricular dilation reduced this probability.

Instrumental tests performed prior to implantation were taken into account: The dobutamine stress echocardiogram allowed to evaluate the absence of left ventricular "contractile reserve" that predicts a lower likelihood of CRT response.[5]

Cardiac magnetic resonance imaging confirmed the morphological and functional data of echocardiogram and allowed an analysis of the left intraventricular dyssynchrony, performed through the volume/time curve and its derivative (Figure 1); this analysis showed a "flat peak" morphology curve, associated with an intermediate response to CRT; cMRI also showed areas of myocardial fibrosis in the subepicardial site.

These data are to be integrated with the clinical history of the patient, suffering from a lung cancer for 10 years, treated with cycles of chemotherapy and radiotherapy; he had developed a dilated cardiomyopathy likely to be related to chemotherapy cardiotoxicity, not responsive to optimized medical therapy for heart failure, or regressed after discontinuation of oncologic therapy. Therefore, the presence of cancer therapeutics-related cardiac dysfunction (CTRCD) was outlined. This pattern is frequently characterized by the presence of areas of subepicardial fibrosis identified by the late gadolinium enhancement (LGE) and is associated with a worse prognosis and with a reduced probability of response to both medical therapy and CRT.[6]

We opted for the implantation of CRT-D with a quadripolar left ventricular lead, the latter was implanted in an inferior-lateral vein, and it was decided to activate the MPP mode since the moment of implantation.

Multipoint pacing is a stimulation modality that aims to determine a more rapid and more physiological activation of left ventricle than traditional single-site stimulation, through the implantation of a quadripolar left ventricular lead.

The use of MPP is not currently indicated by ESC Guidelines. Encouraging data came from recent studies (Table 1)[7] that have shown that MPP with a quadripolar lead

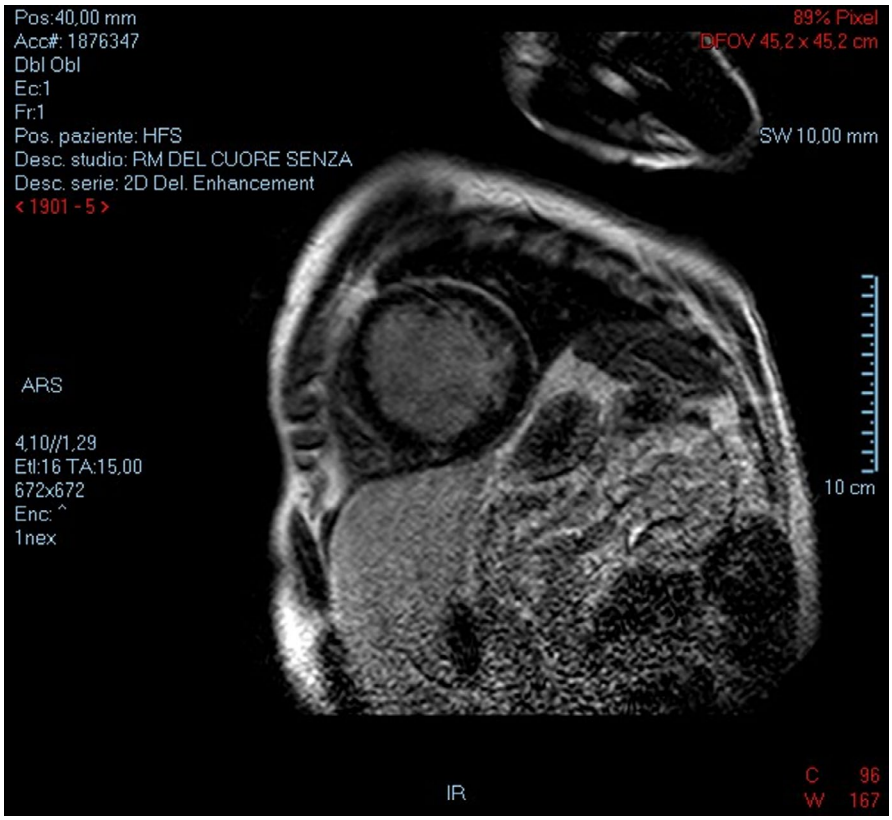


**FIGURE 2** There are small areas of subepicardial late gadolinium hyperenhancement at the basal level of the anterolateral and inferior front walls

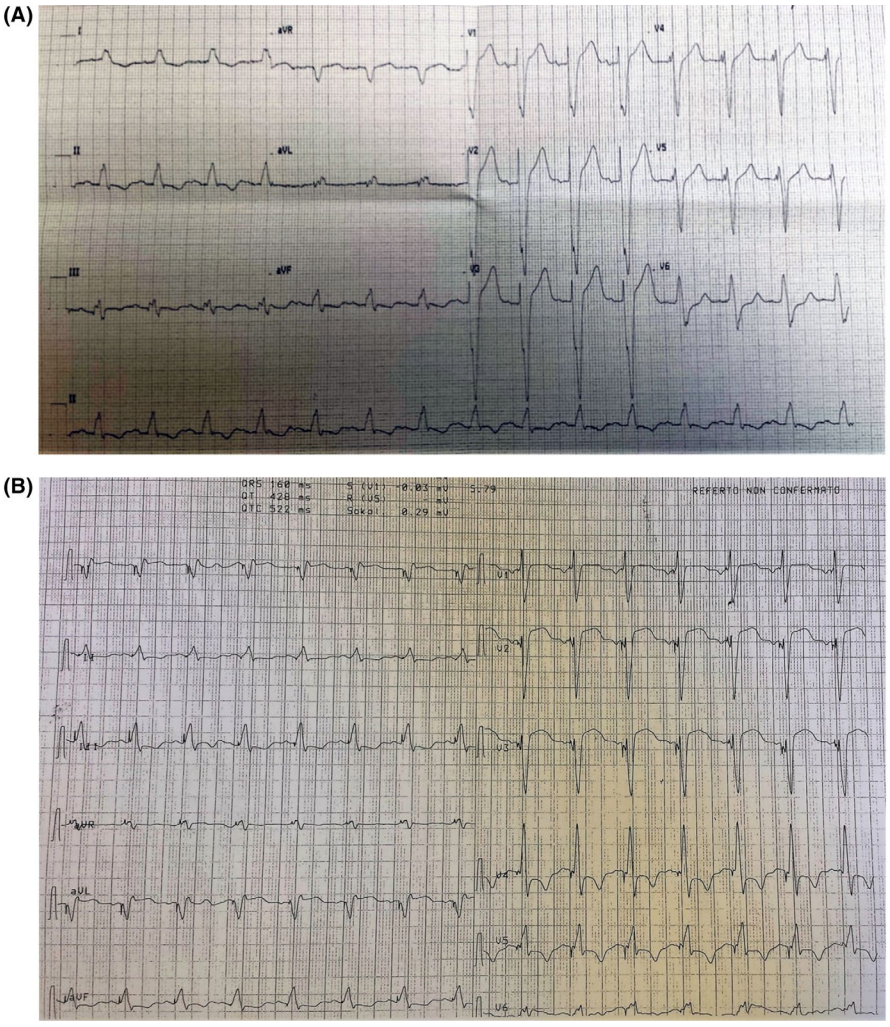


**FIGURE 3** ECG before (A) and after (B) CRT-D implantation. After CRT-D implantation with MPP modality, there is a slight but significant reduction in the duration of the QRS

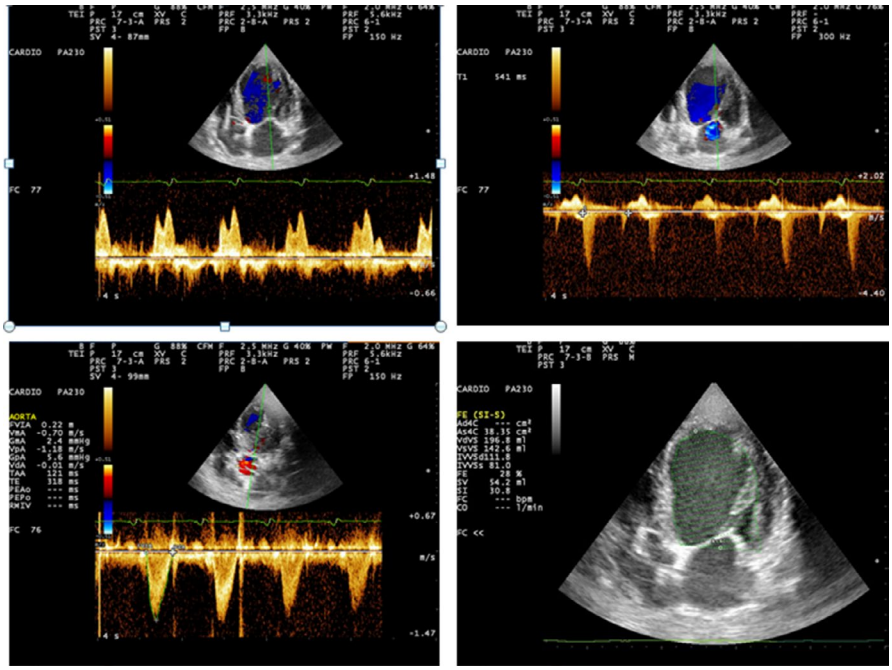

**FIGURE 4** Transmitral diastolic filling pattern, Doppler trace related to mitral regurgitation, velocity time integral (VTI) in the left ventricular outflow tract and 4-chamber apical projection with the telediastolic and telesystolic volumes of the left ventricle after CRT-D implantation with MPP modality are noted in the four squares

**TABLE 1** Studies of multipoint pacing (MPP) through a quadripolar left catheter

| Author (year) | Number of patients | Type of study | Results |
|---|---|---|---|
| Thibault et al (2013)[8] | 19 (21) | Comparative study in acute setting<br>Measurements: invasive hemodynamic evaluation (d*P*/d*t*) | In 72% of patients, MPP improved systolic function in acute vs conventional CRT. Pacing through the most distal and most proximal electrodes generally provided the best d*P*/d*t* |
| Rinaldi et al (2013)[9] | 41 (52) | Postimplant comparative study<br>Measurements: dyssynchrony measured by echocardiogram (TDI) | In 64% of patients, MPP provided a significant reduction in dyssynchrony vs conventional CRT |
| Pappone et al (2014)[10] | 44 | Comparative randomized study at the implant, monocentric<br>Measurements: evaluation of CRT response (ESV reduction ≥ 15%) | After 12 mo of implantation, 57% of patients with conventional CRT and 76% of patients with MPP were classified as responders ($P = 0.33$) |
| Behar et al (2015)[11] | 721 | Multicentric registry<br>Measurements: quadripolar lead performance and 5-y mortality | CRT with MPP (and quadripolar lead implantation) is associated with less stimulation of the phrenic nerve and with less overall mortality (13.2% vs 22.5%, $P < 0.001$) 5 y after implantation than conventional CRT with bipolar lead. |
| Forleo et al (2016)[12] | 507 (232) | Multicentric registry, 46% of patients discharged with active MPP and 54% with nonactive MPP<br>Measurements: (a) modification of LVEF at 6 mo from implantation, (b) clinical response to heart failure (score) | After 6 mo, LVEF was significantly higher in patients with active MPP compared to conventional CRT ($P < 0.001$)<br>After 6 mo, significant improvement in the clinical score was observed in patients with active MPP compared to conventional CRT ($P = 0.009$) |
| Turakhia et al (2016)[13] | 23.570 | Retrospective observational study<br>Primary outcome: 1-y mortality among patients who underwent CRT implantation with a quadripolar vs bipolar electrode | One year after implantation, patients with a quadripolar lead (and MPP) had lower mortality (HR: 0.77; 95% CI: 0.69-0.86; $P < 0.001$) and lower risk of deactivation (HR: 0.62; 95% CI: 0.46-0.84; $P = 0.002$) or lead replacement (HR: 0.67; 95% CI: 0.55-0.83; $P < 0.001$) compared to patients with bipolar lead and conventional CRT |
| Niazi et al (2017)[14] | 381 | Prospective multicenter prospective study. CRT system in BiV mode. A 3-mo randomization 1:1 in BiV vs MPP stimulation | After 6 mo of follow-up, the primary safety endpoint (freedom from system complications) and the primary efficacy endpoint (noninferiority of MPP compared to BiV for the percentage of nonresponders) were reached |
| Behar et al (2017)[15] | 606 | Multicentric retrospective observational study<br>Cost-effectiveness analysis of CRTs with quadripolar electrodes compared to the bipolar ones | Patients with quadripolar lead and MPP had a lower rate of hospitalization (42.6% vs 55.4%; $P = 0.002$) attributable to a lower number of hospitalizations for heart failure ($P = 0.003$) and lower rate of hospitalization for replacement of the generator ($P = 0.03$) than those with conventional CRT<br>The higher initial cost of the CRT-MPP with quadripolar lead is offset by lower costs in the 5 y following the implant (for the average additional price of £1200 [US $1800] over a bipolar system, the incremental cost-effective ratio was £3692 per quality-adjusted life-year gained [US $5538]) |
| Leyva et al (2017)[16] | 847 | Retrospective observational study<br>Evaluation of clinical outcomes in patients with CRT with quadripolar leads compared to CRT with nonquadripolar leads with stimulation of a single LV site | CRT with quadripolar leads is associated with lower total mortality, cardiovascular mortality, and heart failure hospitalization |
| Leshem et al (2018)[17] | 2913 | Prospective observational study comparing CRT with quadripolar leads and conventional CRT with bipolar leads<br>Primary endpoint: hospitalization rate for heart failure | No significant difference in the rate of hospitalization for heart failure was observed |

Abbreviations: BiV, biventricular stimulation; CI, confidence interval; CRT, cardiac resynchronization therapy; d*P*/d*t*, rate of rise of left ventricular pressure; ESV, end-systolic volume; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; TDI, tissue Doppler imaging.

implantation was associated with fewer hospitalizations for heart failure (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.33-0.50; $P < 0.00001$), higher rate of response to resynchronization in terms of improvement of LVEF (mean difference, 4.97; 95% CI, 3.11-6.83; $P < 0.00001$), and reduction in morbidity for all causes (OR, 0.41; 95% CI, 0.26-0.66; $P = 0.0002$) and in cardiovascular-cause mortality (OR, 0.21; 95% CI, 0.11-0.40; $P < 0.00001$).[8-17] Cost-effectiveness studies[15,18] also demonstrated that the higher initial cost of this stimulation system is subsequently offset by savings in the 5 years following the implantation, due to the reduction in hospitalization rates. In light of this evidence, the MPP mode, despite the need for better validation, appears to be a clinically advantageous and economically sustainable strategy.

In our case, the patient showed improvement of functional capacity and of left ventricular function, and reduction in left ventricular volumes, the degree of mitral regurgitation, and the QRS duration even if, in our case, we do not have available data on the possible clinical and instrumental progress of the same patient with eventual only biventricular stimulation, and patient follow-up was not adequately long due to his unexpected death.

Current guidelines do not strictly recommend either performing stress echocardiogram or cMRI prior to implantation of CRT, although such examinations may be considered in some clinical settings.

Further studies are needed to reduce the high number of nonresponders to CRT. In our opinion, to achieve this aim are necessary appropriate clinical evaluation of the patient and choice of appropriate diagnostic tests that allow to predict the most effective and most suitable stimulation modality for the single patient. MPP and quadripolar lead implantation could be a valid option in cases where an adequate response to CRT is not expected.

## CONFLICT OF INTEREST

None declared.

## AUTHOR CONTRIBUTIONS

CM: was the cardiologist who first saw the patient in the clinic, followed his case, admitted him, and indicated the CRT-D MPP implant. LC: was the cardiologist who gave technical and bibliographic support to the writing of the article. EDG: was the first operator surgeon in the CRT-D MPP plant, at the operating unit of which he is director.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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