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Discontinuation of Cardiac Resynchronization Therapy for Heart Failure Due to Dilated Cardiomyopathy in a 61-Year-Old Female "Super-Responder" with Return of a Reduced Left Ventricular Ejection Fraction to Normal

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 61-year-old
Final Diagnosis: Dilated cardiomyopathy
Symptoms: Dyspnea on exertion
Medication: —
Clinical Procedure: Medications and CRT
Specialty: Cardiology

Objective: Unusual clinical course

Background: Although cardiac resynchronization therapy (CRT) is widely used, it has been validated only during active pacing. "Super-responders" are patients with normalized or markedly improved left ventricular (LV) systolic function with CRT who may experience a decline in cardiac function with CRT discontinuation.

Case Report: A 61-year-old woman with a nonischemic cardiomyopathy was admitted to our hospital in September 2008 for the treatment of heart failure (HF). Cardiac assessment revealed impaired LV function with an ejection fraction of 18%, LV dilatation, and left bundle branch block (LBBB). Despite optimized medical treatment, her HF progressed, with a rapid increase in LV chamber size, mitral regurgitation, and widening of the QRS complex. In July 2011, the patient initially refused CRT, but later consented to the procedure; CRT pacemaker implantation was subsequently performed. Thereafter, the LVEF improved from 27% to 46%, LV diastolic dimension decreased rapidly from 79 mm to 56 mm, and LVEF (65%) and LV size (47 mm) normalized within 1 year later. As of August 2012, battery exchange was needed within 1 year because of high LV pacing thresholds. In October 2012, although CRT discontinuation was not recommended, we discontinued CRT to conserve battery life with the patient's consent, hoping to maintain her condition with pharmaceutical treatment. She remained stable through January 2020, with no indication of re-exacerbation.

Conclusions: We describe a female patient with a nonischemic cardiomyopathy and LBBB who demonstrated a super-response to CRT and maintained improvement in LV function and functional status for 8 years after discontinuing CRT.

MeSH Keywords: Ventricular Remodeling • Cardiac Resynchronization Therapy • Cardiomyopathy, Dilated

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Background

Cardiac resynchronization therapy (CRT) is a treatment option for heart failure (HF) in patients with a reduced ejection fraction (EF) (≤35%) and intraventricular conduction delay (especially left bundle branch block [LBBB]), who are refractory to medication alone. Symptomatic HF is characterized by symptoms (e.g., breathlessness, ankle swelling, and fatigue) caused by a structural and/or functional cardiac abnormality. LBBB is a cardiac conduction abnormality seen on electrocardiography (ECG) that is mostly due to cardiac abnormality, and the QRS duration on ECG must be >120 ms. CRT has been reported to increase the left ventricular (LV) ejection fraction (LVEF), reduce LV size, and improve symptoms [1,2]; however, approximately 70% of patients benefit from CRT [3]. Patients are normally classified as either responders or nonresponders based on changes in the LVEF, LV size, and clinical symptoms, although unified definitions of CRT response and nonresponse have not yet been established [3,4]. Additionally, the concept of a CRT super-response has recently been introduced; this has been defined as an improvement in LVEF to >50% and/or a decrease in LV size of >25–30% by 6 months to 1 year after implantation [4,5]. Super-responders may also react differently to CRT discontinuation by exhibiting a rapid decrease in the LVEF and an increase in both mitral regurgitation (MR) and QRS complex width [6,7].

Some studies have reported that discontinuation of CRT results in a decline in cardiac function due to recurrence of remodeling, even in super-responders [5,6]; therefore, CRT should be continued as long as possible. Here, we report a case of dilated cardiomyopathy (DCM) treated with CRT and medication in which the patient, classified as a CRT super-responder, was able to successfully discontinue CRT.

Case Report

A 61-year-old woman with no medical history was admitted to our hospital in September 2008 for 2 months of progressive dyspnea. She was documented to have decompensated HF with New York Heart Association (NYHA) II functional limitations. She had no history of tobacco smoking, alcohol consumption, or substance abuse. Results of the physical examination were: height, 150 cm; weight, 42 kg; body mass index (BMI), 18.7 kg/m^2; blood pressure, 120/66 mmHg; heart rate, 73 beats/min; and oxygen saturation, 94% (room air). Her dyspnea on exertion was class II based on the NYHA classification. On auscultation, a third heart sound (S3) and an apical systolic murmur were detected.

Chest radiography revealed cardiomegaly and bilateral pleural effusions. ECG showed a sinus rhythm with LBBB and a QRS complex duration of 140 ms (Figure 1A–1E). Echocardiography

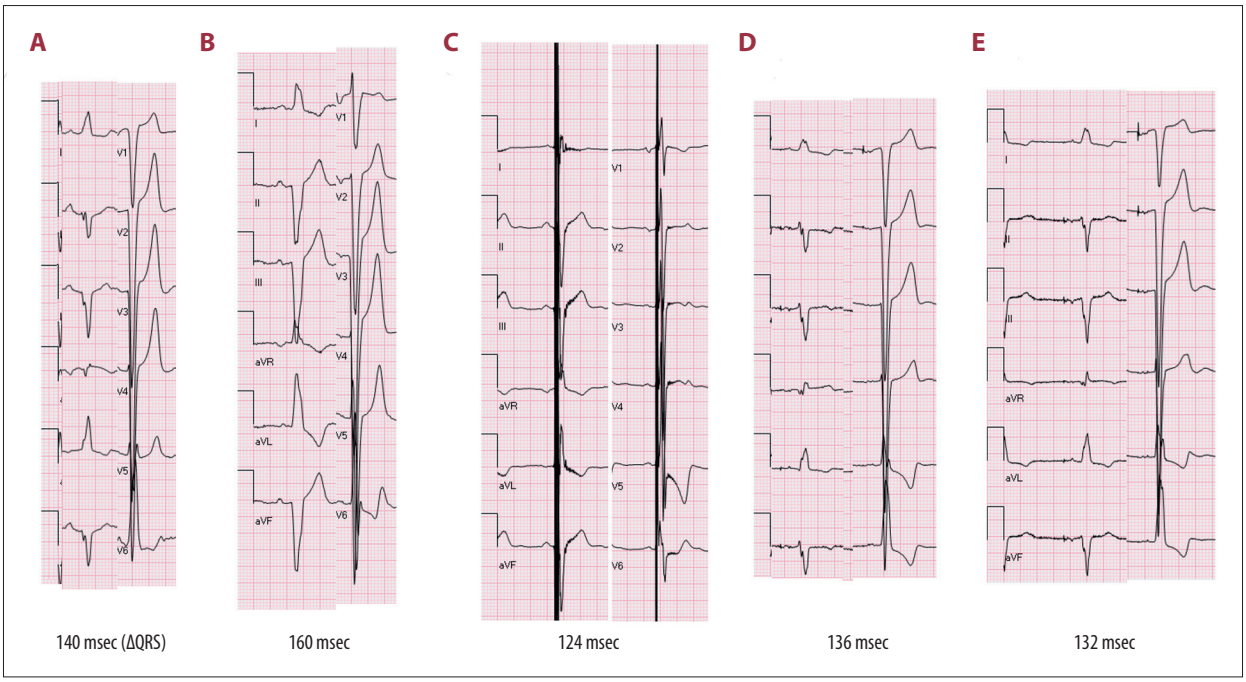

Figure 1. Changes in electrocardiogram parameters (QRS complex) over the course of the treatment. (**A**) Initial assessment. (**B**) Third admission (just before CRT pacemaker implantation). (**C**) Immediately after implantation of CRT pacemaker implantation (biventricular pacing). (**D**) Immediately after discontinuation of CRT. (**E**) Most recent assessment, 6 years after CRT discontinuation. CRT – cardiac resynchronization therapy.

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revealed severe LV enlargement with impaired systolic function and an LVEF of 18% (normal range, 55–65%). LV diastolic to systolic dimension (LVDd/LVDs) was 56/48 mm (normal range, 40–55/30–45 mm), and moderate MR was observed. Based on these findings, the patient was admitted with a diagnosis of HF.

Secondary cardiomyopathy associated with autoimmune disease, metabolic disease, and inflammatory disease may show echocardiographic findings similar to DCM. Blood tests results were normal and ruled out these diseases. Coronary angiography was also performed to exclude ischemic cardiomyopathy, and it did not demonstrate significant coronary artery disease. Cardiac magnetic resonance imaging demonstrated LV dilation with an LVEF of 16% and no evidence of abnormal gadolinium enhancement. Thus, no findings were suggestive of secondary cardiomyopathy after these examinations. Along with these results, and based on the 2006 American Heart Association Classification of "Contemporary definitions and classification of the cardiomyopathies," we reached a final diagnosis of DCM.

Diuretic treatment was initiated (furosemide: 40 mg/day, initially administered via intravenous injection and then orally) in combination with an angiotensin II receptor blocker (candesartan: 4 mg/day) and a β-blocker (carvedilol) for secondary prevention of HF. As the prognostic improvement associated with β-blockers is dose-dependent, the guidelines recommended increasing the dosage in accordance with the tolerance level of the patient [8,9]. In our case, the carvedilol dosage was increased to 10 mg/day. The use of mineralocorticoid/aldosterone receptor antagonists and a further increase in the carvedilol dosage were not possible because of hypotension. The patient's HF improved, and she was subsequently discharged.

In October 2009, the patient was readmitted because of HF re-exacerbation, despite ongoing pharmaceutical treatment. Echocardiography revealed an LVEF of 30% and an LVDd/LVDs of 67/54 mm, and ECG indicated a QRS width of 144 ms. We determined that CRT was required; however, the patient refused because of fear of surgery. Hence, pharmaceutical treatment alone was continued. In June 2011, the patient's HF worsened, and she was readmitted with significant widening of the QRS complex (160 ms), decreased LVEF (27%), and rapidly increased LVDd/LVDs (79/69 mm). In July 2011, she consented to CRT, and a pacemaker (AllureTM, St Jude Medical, MN, USA) was implanted. The placement of the LV leads resulted in a high LV pacing threshold; however, no other positions were feasible because there was no other coronary vein branch wherein the LV lead could be inserted with a good threshold. Immediately after implantation, the LVEF increased and QRS width decreased.

Echocardiography performed in August 2011 revealed significant improvements in both the LVEF (46%) and LV enlargement (LVDd/Ds of 56/43 mm), the QRS width was 124 ms, and we were able to increase the carvedilol dosage to 20 mg/day. Follow-up echocardiography performed in June 2012 confirmed the improvement in the LVEF (65%) and LVDd/LVDs (47/30 mm), revealed QRS width of 136 ms, and showed mild MR.

At this point, due to the high threshold of the LV pacing lead, the remaining battery power was estimated to last less than 1 year; thus, we decided to discontinue biventricular pacing. Although the LBBB persisted, follow-up ECG and echocardiography indicated that the QRS width had not increased (136 ms) and there was no deterioration in MR or LVEF. Therefore, with the patient's consent, CRT was discontinued in October 2012 to preserve the battery. We changed the mode from DDD to AAI as there was a mild bradycardia, possibly due to the increased β-blocker dose. It was clearly communicated to the patient that CRT would be promptly restarted if there was any sign of HF re-exacerbation; she was carefully monitored for the following 4 years, during which there was no deterioration of cardiac function. Echocardiography and ECG revealed an LVEF of 69%, LVDd/LVDs of 44/27 mm, and a QRS width of 130 ms during follow-up in August 2014, and an LVEF of 60%, LVDd/LVDs of 42/30 mm, and a QRS width of 126 ms in June 2016. The latest follow-up in November 2018 revealed an LVEF of 64%, LVDd/LVDs of 44/30 mm, and a QRS width of 132 ms.

In anticipation of probable cardiac remodeling that could re-exacerbate the HF, and thus require prompt resumption of CRT, a generator exchange surgery was performed in June 2016. At the most recent follow-up in 2020, CRT had not been resumed and the patient's status remained stable without signs of re-exacerbation (Figure 2A, 2B).

Discussion

CRT has been reported to improve symptoms and mortality in patients with HF who present with prolongation of the QRS complex and low LVEF despite standard medical therapy [1,2]. Approximately 60–70% of patients respond to CRT [10,11]. CRT responders show that the beneficial clinical outcomes are due in part to significant reductions in the LV end-systolic volume, so-called reverse remodeling (RR), and the occurrence of RR is closely related to prognosis [4]. It is considered that RR occurred in this case, resulting in the improvement in LVEF and LV size. Additionally, a high degree of RR may have made this case a super-responder. Further, this case is characterized by an extremely fast rate of improvement, as can be seen from the fact that the EF improved from 27% to 46% and the LVDd/LVDs decreased from 79/69 mm to 56/43 mm within 1 month of CRT. This may be because RR progressed rapidly.

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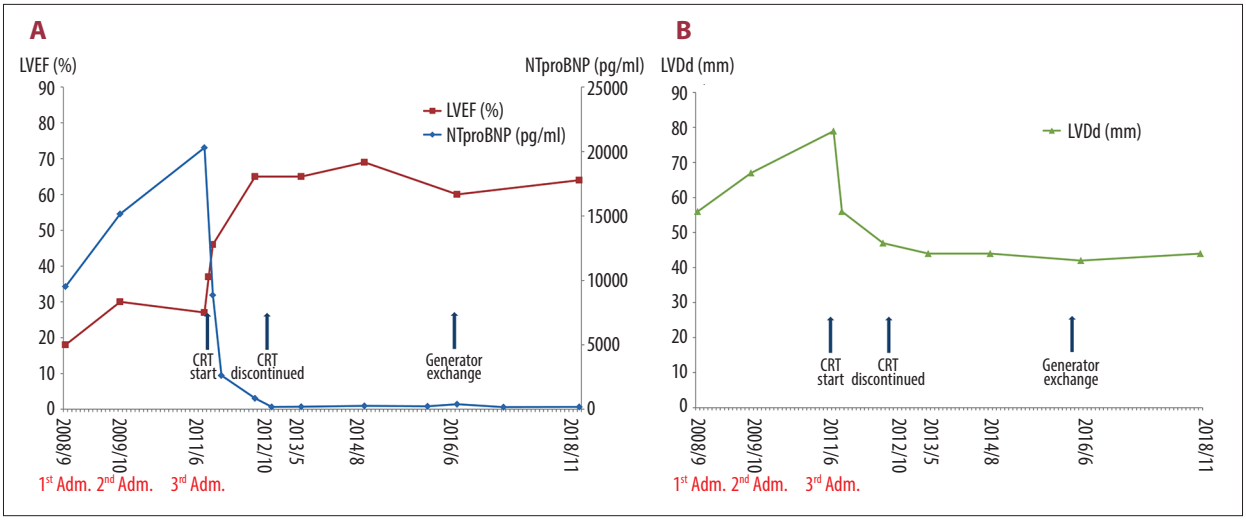

Figure 2. Change in each parameter and events that occurred over the course of treatment. (**A**) LVEF, NT-pro BNP, (**B**) LVDd. LVEF – left ventricular ejection fraction; LVDd – left ventricular diastolic dimension; NT-pro BNP – NT-proB-type natriuretic peptide.

Hsu et al. reported that a QRS duration of ≥150 ms, LBBB, BMI <30 kg/m^2, and smaller baseline left atrial volume index, as well as being female and having no prior myocardial infarction, were all predictors of a CRT super-response [12]. This case was classified as a super-responder. Remarkably, this patient met all of these criteria, which may have been the reason for the high and rapid RR.

Standard, evidence-based medical treatments for HF with a low EF have included β-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid/aldosterone receptor antagonists [9]. Among these drugs, β-blockers promote RR to the greatest extent [13]. In many patients, it is possible to increase the β-blocker dosage up to that recommended by the guidelines after CRT; however, such an increase is not possible before CRT [14,15]. Thus, the stable outcome of our patient after CRT discontinuation may have been related to the increased dosage of β-blockers after CRT. These factors may explain the high degree of RR progression.

In this case, we also noticed that the improvement of the EF was accompanied by shortening of the QRS width, and even after CRT was discontinued, the QRS width did not increase again. It is hypothesized that an increase in the QRS width indicates electrical remodeling, whereas a decrease in the EF indicates mechanical remodeling. Shortening of the QRS width in our case may have implied electrical RR, and the lack of reincrease in the QRS width may be due to the absence of electrical RR recurrence following discontinuation of CRT.

Another study demonstrated that prolonged mechanical dyssynchrony as a result of the LBBB may have triggered mechanical and electrical remodeling [16]. CRT is reported to improve both electrical and mechanical remodeling by modifying mechanical dyssynchrony. In our case, indeed, it seemed that high degrees of electrical and mechanical RR had occurred.

Liang et al. demonstrated that even super-responders sometimes exhibited a recurrence of electrical and mechanical remodeling after CRT discontinuation [5]; therefore, CRT should be continued when possible to promote these protective factors. In our patient, CRT was discontinued because of the high rate of battery consumption; however, this was a special case, and current evidence and guidelines do not recommend the discontinuation of CRT.

A previous study reported that CRT was interrupted in approximately 4–10% of the patients for various reasons (this excludes interruption due to arrhythmias and includes only those caused by device or lead issues) [17,18]. In such cases, CRT should be continued in accordance with guidelines and supporting evidence, using methods such as reoperation. There may be cases where it is difficult to continue CRT for various reasons. We believe our case is unique, as it demonstrates that remodeling may not occur despite discontinuation of CRT. However, because of limited data, we cannot elucidate the mechanisms involved. Many studies and guidelines have recommended that CRT should be continued as long as possible [5,6,19] and discontinuation is not recommended. In this case, although CRT was discontinued, good results were achieved, and HF did not recur.

Conclusions

We present a rare case of DCM treated with CRT and medication in a female patient who demonstrated a super-response to CRT and was able to successfully discontinue CRT without

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re-exacerbation of HF. Guidelines and evidence do not recommend discontinuation of CRT; however, there have been reports of patients who have had difficulty continuing CRT for various reasons. As in this case, super-responders or those with rapidly progressing RR may be suitable for CRT discontinuation. Nevertheless, clear indicators for discontinuing CRT are currently unknown because of a lack of evidence.

We hope that this case will provide evidence for similar studies in the field and assist in the identification of alternative treatment strategies for cardiomyopathy, as we have considered these results to be not only exceptional, but also interesting and impressive.

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Conflict of interest

None.

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