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Case Reports

Cardiac Resynchronization Therapy (CRT) Optimization: A Way Out for Non-Responders - A Case Report

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Abstract

Background: Non-responders account for 30% of patients receiving Cardiac Resynchronization Therapy (CRT). Optimization of CRT using Electrocardiographic (ECG) and Transthoracic Echocardiographic (TTE) guidance has been proposed as a strategy to enhance therapeutic efficacy in this subset. This case report presents a young female patient with advanced heart failure secondary to ischemic cardiomyopathy, highlighting the role of ECG- and TTE-guided CRT optimization in improving clinical and hemodynamic outcomes.

Case Illustration: A 37-year-old female presented with advanced heart failure. Her medical history was notable for recurrent episodes of acute coronary syndrome, multiple Percutaneous Coronary Interventions (PCIs), and Cardiac Resynchronization Therapy with Pacemaker (CRT-P) implantation, despite adherence to Guideline-Directed Medical Therapy (GDMT).

On admission, the ECG demonstrated atrial sensing with consistent Biventricular (BV) pacing. Laboratory evaluation revealed an elevated N-terminal pro–B-type natriuretic peptide (NT-proBNP) level of 5.462 pg/mL. TTE showed a severely reduced Left Ventricular Ejection Fraction (LVEF) of 20% and an absent A wave on mitral inflow Doppler, indicating impaired diastolic filling. Additionally, the Left Ventricular Outflow Tract (LVOT) Velocity Time Integral (VTI) was reduced to 7.4 cm, consistent with low forward stroke volume. Six months after the implantation, CRT optimization was performed using ECG and TTE guidance. Optimization resulted in a reduction of QRS duration to 129 ms, distinct separation of the mitral inflow E and A waves, an increase in LVOT VTI to 10.9 cm, and an improvement in functional capacity to New York Heart Association (NYHA) class III.

Conclusions: CRT optimization, guided by ECG or TTE, is critical in managing non-responders. In this case, it led to improved QRS duration, hemodynamics, and NYHA functional class. Routine reassessment should be considered in patients with persistent symptoms despite optimal GDMT to enhance clinical response.

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Keywords: Non-responder, CRT optimization, ECG guided CRT optimization, TTE guided CRT optimization.

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Introduction

Cardiac Resynchronization Therapy (CRT) is recommended for Heart Failure with reduced Ejection Fraction (HFrEF) with an expansive QRS complex because it improves myocardial function by resynchronizing myocardial contraction, resulting in reverse left ventricular remodeling.[1] However, almost one-third of patients are Non-Responders (NR), and only half of this group will survive four years after implantation.[2-3] NR is defined by one or more of the following criteria: worsening symptoms of heart failure after receiving CRT, no improvement in functional classification, and increased ventricular remodeling after 6 months of CRT placement, or worsening symptoms after previously responding.[4]

CRT optimization can be performed using several methods, such as Echocardiography (ECG)- or Transthoracic Echocardiographic (TTE)-guided approaches. TTE guidance can be achieved by assessing mitral inflow, Left Ventricular (LV) Outflow Tract (LVOT) Velocity Time Integral (VTI), which reflects the most significant stroke volume, tissue Doppler imaging (TDI), M-mode, or strain measurement. ECG guidance involves evaluating the QRS-based approach, 12-lead ECG, and Fusion-Optimized Intervals (FOI).[5]

This case presentation aims to describe CRT optimization guided by ECG and TTE in a patient with HFrEF secondary to ischemic cardiomyopathy.

Case Illustration

A 37-year-old female patient came to the emergency room with worsening symptoms of heart failure, such as shortness of breath, swelling in both legs, and a bloated stomach for one week before admission. She had a history of Acute Coronary Syndrome (ACS) in 2018 and 2020, underwent Percutaneous Coronary Intervention (PCI) with one Drug-Eluting Stent (DES) in the Left Anterior Descending (LAD) and Left Main-Left Circumflex (LM-LCx) in 2018 and 2021, respectively, and received a Cardiac Resynchronization Therapy Pacemaker (CRT-P) in April 2021. Her medications included Sacubitril/Valsartan 7 mg twice daily, Carvedilol 12.5 mg twice daily, Amiodarone 200 mg once daily, Furosemide 40 mg twice daily, Tolvaptan 7.5 mg twice daily, Atorvastatin 20 mg once daily, Spironolactone 25 mg once daily, Clopidogrel 75 mg once daily, and Aspirin 80 mg once daily.

Physical examination revealed increased jugular venous pressure, positive hepatojugular reflex, a pansystolic murmur 3/6 on the left lateral sternal border, rales in the lower third of the lungs, ascites, and pitting edema in both legs. ECG showed atrial sensing and Biventricular (BV) pacing (R wave in aVR and Rs in V1) with a QRS rate of 90 bpm and a QRS duration of 160 ms. Laboratory examination showed creatinine 1.23 mg/dl, Estimated Glomerular Filtration Rate (eGFR) 49, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) 5462 pg/ml. Chest X-ray revealed cardiomegaly with signs of congestion. Echocardiography showed a Left Ventricular Ejection Fraction (LVEF) of 20%, Tricuspid Annular Plane Systolic Excursion (TAPSE) of 1.6 cm, global hypokinesis, dilatation of all chambers, eccentric Left Ventricular Hypertrophy (LVH), moderate to severe Mitral Regurgitation (MR) due to the tethering of the Posterior Mitral Leaflet (PML), moderate Tricuspid Regurgitation

Table 1. CRT optimization with TTE guided.

	1	2	3	4	5	6	7	8	9
AV Delay (ms)	120/110	120/110	120/110	120/110	120/110	130/130 Syn AV on -30 ms	130/130 Syn AV on -20ms	130/130 Syn AV on - 10 ms	130/130 Syn AV on -10 ms
V-V synchrony (ms)	LV (D1/ mid2) to RV 0 ms (simultant)	LV (D1-mid2) to RV 30 ms	LV (D1-mid2) to RV 30 ms	LV (D1-mid2) to RV 60 ms	LV (D1-mid2) to RV 60 ms	LV(D1-P4) to RV 60 ms	LV(D1-P4) to RV 60 ms	LV(D1-P4) to RV 60 ms	LV (D1-P4) to RV 30 ms
LVOT VTI (cm)	7.2	10.2	6.8	9.6	10.7	9.7	10.9	-	9.6
E/A	separated	separated	separated	separated	separated	separated	separated clearly, E/A 3.2	separated	separated
QRSd (ms)	321	153	167	129	129	129	129	128	151

AV: atrioventricular; CRT: Cardiac Resynchronization Therapy; D: Distal; LV: Left Ventricle; LVOT VTI: Left Ventricular Outflow Tract Velocity Time Integral; P: Proximal; QRSd: QRS duration; Syn: Synchrony; TTE: Transthoracic Echocardiography; VV: Ventriculo-Ventricular

(TR) with TVG of 26 mmHg, and mild Pulmonary Regurgitation (PR) with a Mean Pulmonary Arterial Pressure (mPAP) of 60 mmHg.

During hospitalization, the patient complained of fatigue, and her blood pressure dropped to 60/45 (50) mmHg, leading to adjustments in her antihypertensive medications. The first attempt at CRT-P optimization guided by TTE was planned six months after implantation. Multiple attempts at Atrioventricular (AV) delay, and Ventriculo-Ventricular (VV) synchrony settings using a programmer machine were performed simultaneously with the measurement of LVOT VTI and mitral inflow E/A using TTE, as well as the measurement of QRS duration using ECG. The optimal parameter for the CRT-P was a Syn AV offset of -20 ms and an LV pacing configuration from D1 to P4, with a 60 ms delay relative to right ventricular pacing. These AV delay and VV synchrony settings showed clearly separated E/A of 3.2, LVOT VTI of 10.9 cm, and QRS duration of 129 ms, as shown in Table 1 and Figure 1.

The patient's condition improved with a blood pressure of 90/56 (67) mmHg. One month after CRT optimization, she had stable hemodynamics and an improved New York Heart Association (NYHA) functional class, classified as III. ECG showed atrial sensing and BV pacing-fusion with a shorter QRS duration of 129 ms (Figure 2), and echocardiography revealed clearly separated E and A waves.

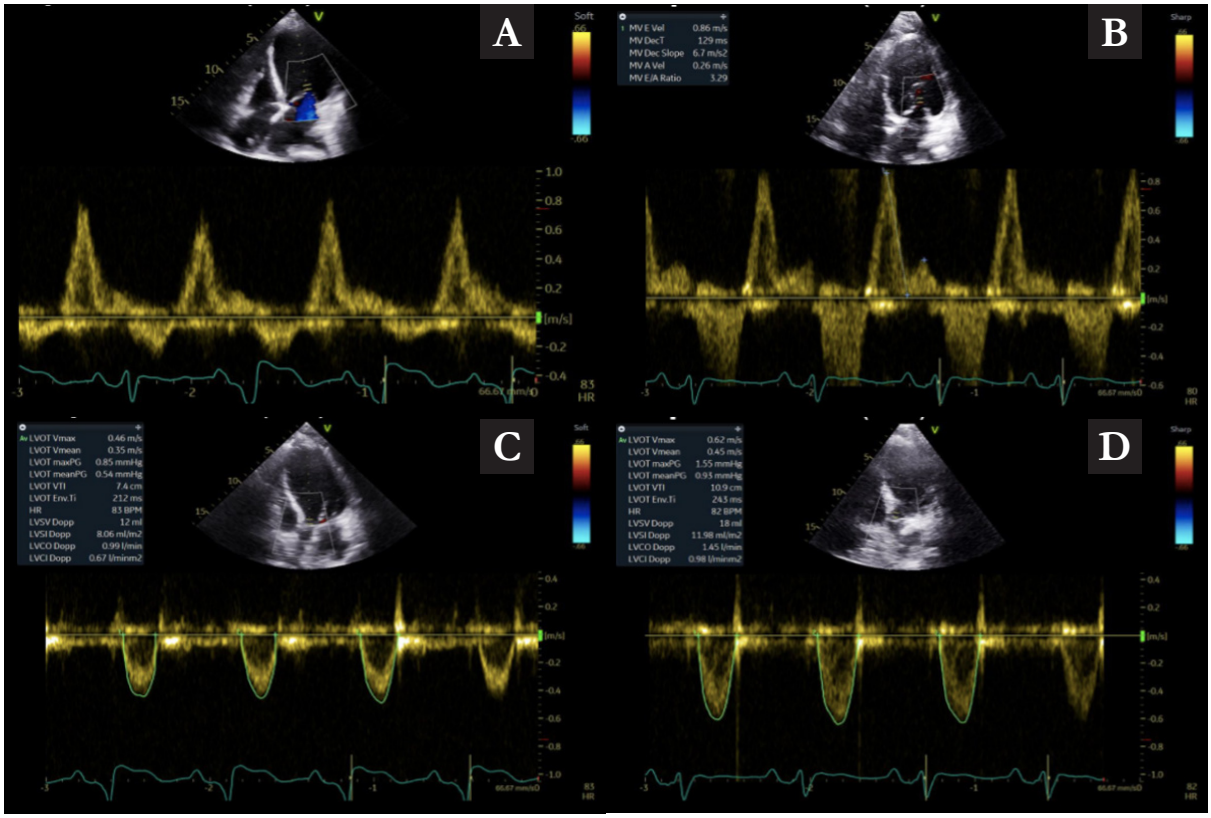

Figure 1. (A) E/A before CRT optimization; (B) E/A after CRT optimization; (C) LVOT VTI before CRT optimization; (D) LVOT VTI after CRT optimization.

Discussion

CRT is one of the most important treatments for drug-refractory heart failure. CRT aims to correct the three types of cardiac dyssynchronous activation through BV pacemaker stimulation, thereby improving LV hemodynamic and cardiac efficiency. CRT response is defined by three categories: clinical measurement assessment, LV reverse remodeling assessment, and outcome measure assessment. It has been suggested that response rates are higher when clinical measures are used rather than LV remodeling or outcome measures. Additionally, several factors have been associated with a greater benefit from CRT, including female sex, QRS width >150 ms, Left Bundle Branch Block (LBBB) morphology, and non-ischemic etiology.[4,6]

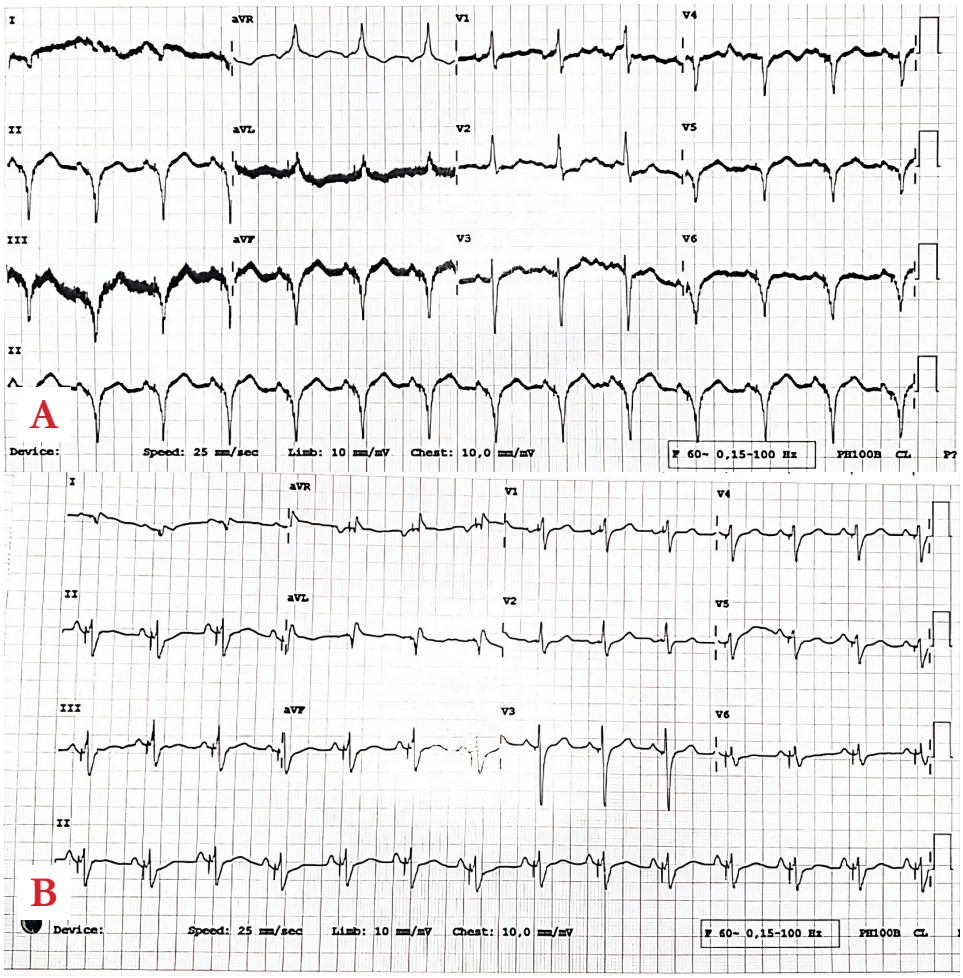

Figure 2. ECG before (A) and after CRT optimization showing BV pacing – fusion with shorter QRS duration (B).

This case highlights the uncommon presentation of ischemic cardiomyopathy in a young female patient. While younger age is generally associated with better outcomes in CRT, factors such as myocardial fibrosis, left ventricular lead positioning, and the underlying etiology of cardiomyopathy can significantly influence the response to therapy.[7] The patient was considered a non-responder due to worsening symptoms even after CRT placement, with NYHA class IV criteria. Additionally, LV reverse remodeling assessment in the acute setting showed an LVOT VTI of 7.4 cm, resulting in low cardiac output. Outcome measurement indicated hospitalization due to acute heart failure. Therefore, optimization of CRT was needed to address these issues. The ischemic cardiomyopathy etiology of the heart failure in this patient resulted in less benefit from CRT.

In ischemic cardiomyopathy, non-response to CRT is commonly attributed to two key factors, namely high myocardial scar burden and limited mechanical recruitment. Extensive or transmural scar tissue limits both electrical capture and mechanical contraction, reducing CRT efficacy. Furthermore, despite successful restoration of electrical synchrony, regions of non-viable myocardium exhibit diminished contractile reserve, thereby attenuating the hemodynamic efficacy of CRT.[8] Therefore, in CRT candidates with ischemic cardiomyopathy, pre-implant viability imaging and scar assessment using Cardiac Magnetic Resonance (CMR), nuclear imaging, or Computed Tomography (CT) are essential for predicting response and guiding lead placement.[9]

Several factors beyond pre-implant patient selection may affect CRT response, including peri-implant lead positioning and lead choice, as well as post-implant factors related to the device and heart failure therapy. Among the many factors contributing to suboptimal CRT response, suboptimal AV timing is the most prevalent. Suboptimal AV timing can be managed through AV and VV optimization using

TTE, ECG, or device-based methods.[10]

Simplified Doppler screening for AV optimization can be performed using pulsed Doppler mitral inflow. AV optimization is recommended if any of the following are observed: the A wave is not identified, the E and A waves are merged, or the A wave is truncated by mitral closure.[11] As shown in this patient's TTE, the A wave was not identified on pulsed Doppler mitral inflow; therefore, AV optimization was required. AV optimization can also be achieved by optimizing LV systolic performance through evaluation of the aortic pulsed-wave Doppler VTI, which correlates with LV stroke volume. Aortic VTI is measured across a range of AV delays, and the delay that yields the most significant increase in VTI is selected as the optimal AV delay.[11-12] The AV delay that was set at -20 ms was considered the setting that led to the greatest LVOT VTI of 10.9 cm compared to the baseline of 7.4 cm.

VV optimization can also be performed using the aortic VTI method, as in AV delay optimization. In this method, aortic VTI is measured at varying intervals of RV and LV preexcitation, with the interval that yields the greatest VTI selected as the optimal VV delay.[12]

ECG provides an additional method to optimize CRT by adjusting both AV and VV delays. ECG parameters used to measure ventricular dyssynchrony include QRS duration and the presence of LBBB. ECG methods for optimizing CRT include the twelve-lead ECG and FOI. The twelve-lead ECG is used to evaluate the morphology rather than the QRS duration of the BV-paced complex. A stepwise increase in AV delay during BV-pacing begins with a short AV delay to identify the onset at which QRS morphology changes. Meanwhile, VV interval programming should be used to create a QRS complex with adequate contribution from LV pacing to maintain a dominant R (R, Rs, or RS pattern) in leads V1-V2.

The FOI method involves finding the fusion band. During atrial sensing, the AV interval is progressively shortened with LV pacing only, starting with the most extended AV interval that allows capture, then decreasing of 20 ms until the AV interval produces only LV capture. The AV interval that provides the narrowest QRS is considered the fusion-optimized AV interval. This is followed by adjusting the VV interval during atrial sensing and comparing QRS duration across configurations. The VV value that obtains the narrowest QRS is considered the fusion-optimized VV interval.5 In this patient, a CRT-P setting of Syn AV on -20 ms and LV (D1-P4) to RV 60 ms led to the shortest QRS duration of 129 ms.

Fusion with intrinsic rhythm during pacing will exhibit three activation fronts compared to the usual pure BV pacing. This fusion pacing is superior to any optimized BV configuration, resulting in improved LV and RV performance.[5] The patient's ECG after CRT optimization showed BV-fusion pacing with a shorter QRS duration of 129 ms than before CRT optimization. The importance of shortening QRS duration can predict a favorable prognosis in patients with LBBB, which is associated with more than two times lower mortality rates. It also serves as a biomarker for the reduction or elimination of asynchronous contraction caused by LBBB. It is a strong predictor of reverse LV electrical remodeling, indicating that the initial goal of CRT implantation has been achieved.[13]

Routine follow-up evaluations should be conducted at 3 months post-implantation and every 6 months thereafter. However, if a persistently widened QRS complex is observed during pacing, incidental optimization of device settings should be considered.[14] Studies have demonstrated that CRT significantly prolongs the time to recurrent hospitalization due to heart failure or all-cause mortality, irrespective of the underlying etiology of cardiomyopathy.[15] In patients with persistent non-response to CRT, several advanced interventions may be considered. Multipoint Pacing (MPP) enhances resynchronization by delivering stimuli from multiple sites within the left ventricular myocardium.[16] Conduction System Pacing (CSP), including His bundle and left bundle branch area pacing, offers a more physiologic alternative to traditional BV pacing.[17] Left ventricular lead repositioning, guided by imaging, can also improve response by targeting viable myocardium and areas of latest activation.[18] In addition, ongoing titration and optimization of Guideline-Directed Medical Therapy (GDMT) remain essential to enhance clinical outcomes.[19]

The integration of ECG and TTE techniques for CRT optimization proves highly valuable, especially in settings with limited resources where access to advanced imaging is restricted. This combined method provides a practical and efficient means to improve CRT efficacy and clinical outcomes under such constraints.

Conclusion

CRT optimization, whether guided by ECG or TTE, is required for managing non-responders. In this case, it resulted in clinical and hemodynamic improvements, including a reduction in QRS duration, enhancement of LVOT VTI, and an improvement in functional status. It is essential to screen for the need for CRT optimization, particularly in patients with refractory heart failure despite optimal GDMT, to enhance clinical response.

List of Abbreviations

ACS	Acute Coronary Syndrome
AV	Atrioventricular
BV	Biventricular
CMR	Cardiac Magnetic Resonance
CRT	Cardiac Resynchronization Therapy
CRT-P	Cardiac Resynchronization Therapy with Pacemaker
CSP	Conduction System Pacing
CT	Computed Tomography
DES	Drug-Eluting Stent
ECG	Electrocardiography
eGFR	Estimated Glomerular Filtration Rate
FOI	Fusion-Optimized Intervals
GDMT	Guideline-Directed Medical Therapy
HFrEF	Heart Failure Reduced Ejection Fraction
LAD	Left Anterior Descending
LBBB	Left Bundle Branch Block
LCx	Left Circumflex
LM	Left Main
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MPAP	Mean Pulmonary Arterial Pressure
MPP	Multipoint Pacing
MR	Mitral Regurgitation
NYHA	New York Heart Association
NT-proBNP	N-terminal pro–B-type natriuretic peptide
PCI	Percutaneous Coronary Intervention
PML	Posterior Mitral Leaflet
TAPSE	Tricuspid Annular Plane Systolic Excursion
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiography
TVG	Tricuspid Valve Gradient
VTI	Velocity Time Integral
V-V	Ventriculo-Ventricular

Ethical Clearance

Informed consent has been obtained from the patient to publish this case report.

Publication Approval

All authors consent to the publication of this manuscript.

Authors Contributions

NED performed the literature search and drafted the original manuscript. DYH supervised the project, and critically revised the manuscript for important intellectual content. Both authors have read and approved the final version of the manuscript.

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Conflict of Interest

The authors declare no conflict of interest.

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Generative AI and AI-Assisted Technologies in the Writing Process

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