Heart Sci J 2020; 1(2): 3-10

Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

Responders vs. Non-responders to Cardiac Resynchronization Therapy

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ARTICLE INFO

Keywords:
Cardiac Resynchronization Therapy;
Responders;
Non-responders

ABSTRACT

More than two decades after the introduction of cardiac resynchronization therapy (CRT) into clinical practice, there was still a challenge to get the expected benefit for this therapy. There was a group of patients that had a good response to the therapy, its called responders group, and others who didn't get expected response called non-responders group. This article will discuss indications for initiating a CRT, the definition of a response to a CRT, steps in response to a CRT, predictors of a CRT response, clinical judgment of patients who do not respond to CRTs, and elimination for possible reversible non-response causes. Here we have reviewed non-response CRTs in many ways. In short, multidisciplinary efforts are needed to overcome them because of the multifactorial causes of non-response (NR). So far, several factors have slowed the progress, such as limitations of NR consensus definitions and technology for therapeutic delivery.

1. Introduction

Cardiac resynchronization therapy (CRT) produces significant clinical benefits and reverse left ventricular (LV) remodeling. In selected patients, CRT can turn cardiac performance better, relieves symptoms, improves well-being, and reduces morbidity and mortality as well. Based on QALY, two-third patient with moderate to severe HF patients with CRT showed improvement in the quality of life and increased longevity;[1] however, 35 – 40% of patients do not show good response.[2] Non-response cardiac resynchronization therapy has multifactorial causes.[3–7]

2. Discussion

2.1 CRT

One of the problems found in severe heart failure patients is the uncoordinated movement of myocardium ventricular dyssynchronies, several dyssynchronies happened. In patients with surface ECG shows LBBB and very dilated LV, we will found interventricular syssynchrony. Uncoordinated movement of the right and left ventricle that results in the decrement of cardiac output. Which will worsen the heart failure itself. CRT therapy act as a regulator to increase coordination in both ventricle thus improves cardiac function, which leads in improvement in the mechanical efficiency of cardiac contraction and relaxation.[9] CRT results in significant clinical benefits and reverse LV remodeling; However, there is no response from 35-40% of patients.[10] Non-response to therapy remained a major problem of Achilles CRT for years, offering many challenges of medical and finance. One contributing factor of non-response cardiac re-synchronization therapy is multifactorial with suboptimal LV lead placement.[10,11] Doctors can optimize the placement of lead LV using intra-cardiac electrograms by finding delayed electrical activation, acute hemodynamic responses measurement, scar location/load, and using electrical or mechanical mapping.[10]

2.2 Indication for starting CRT

The candidates for CRT are patient heart failure (HF) with moderate to severe symptoms despite optimal medical therapy, cardiomyopathy, and significant LBBB. In spite of optimal medical therapy, there is an established remarkable benefit of cardiac resynchronization therapy (CRT) in patients with heart failure (HF) in the functional class II and III New York Heart Association (NYHA) with extensive QRS complexes and reduced left ventricular ejection fraction (LVEF) ≤ 35 %. CRT was highly recommended by all available guidelines for the LBBB case with QRS duration> 150ms. Whereas QRS durations from 120 to 129ms, there is a particular inconsistency between the 2 European Cardiology Societies (ESC). ESC Heart Failure Association (HFA) (2016) states a Class III recommendation ("is not recommended"), while the ESC European Heart Rhythm Association (EHRA) (2013) provides a Class I recommendation ("is recommended"). CCS

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https://doi.org/10.21776/ub.hsj.2020.001.02.2
Received 9 June 2020; Received in revised form 12 June 2020; Accepted 24 June 2020
Available online 18 July 2020

guidelines 2017 was declared that CRT usage was avoided in QRS <130ms. On the contrary, QRS duration with the cutoff set to >120ms in the EHRA guidelines was included in many trials such as CARE-HF (Cardiac Resynchronization-Heart Failure) and COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) as an inclusion criteria.[3,7] After publication ECHO CRT study, there showed an escalation of cardiovascular mortality with CRT in QRS <130ms patients, therefore HF 2016 guidelines set the cutoff to >130ms as an indication for CRT. For non-LBBB patients, ACC/AHA/HRS and ESC guidelines agreed that a CRT "should be considered" (Class IIa), if a patient has a QRS duration >150ms, NYHA functional class III or ambulatory class IV. CCS sets a "may be considered" recommendation (Class IIb) for a similar indication (Table 1). There is considerable inconsistency in the guidelines for non-LBBB and a QRS <150ms patients, between Classes IIb and III recommendations. The CCS guidelines do not provide a formal recommendation for this patient group. However, play explain that there is no clear evidence of benefit with CRT among QRS duration < 150 ms patients caused by non-LBBB conduction. Besides, the level of evidence provided for this group of patients varies even for the same class recommendation.[12-14]

Table 1. Recommendation for cardiac resynchronization therapy implantation in patients with heart failure.[1]

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

Recommendations	Class[a]	Level[b]	Ref[c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; QRS = Q, R and S waves (combination of three of the graphical deflections); RV = right ventricular.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.
[d]Use judgement for patients with end-stage HF who might be managed conservatively rather than with treatments to improve symptoms or prognosis.

2.3 Definition of Response / Non-Response on CRT

2.3.1 Response on CRT

The principal target of HF therapy is to relieve symptoms, restore the quality of life (QOL), slow the progression of the disease, reduce the hospitalization rate, and longevity. Reduction of symptoms and lower morbidity is a primary goal for patients in the New York Heart Association (NYHA) functional Class III and IV HF, and case prevention and inhibit the development of HF is a priority for patients in NYHA Class I and II. The perception and NR for CRT consensus definition have not been reached yet even after 20 years of clinical development. There still a diverse definition in randomized trials vs. clinical practices. The endpoints measured in clinical trials were based on events while unclear criteria are used to assess responses in practice. The definition of response to CRT is also a problem to looking for. The main goal for the patients suffered from severe heart failure is symptom relief with a better quality of life. Though CRT could achieve those goals, expectations develop towards greater social exposure, fewer hospitalizations, and longer survival.[11]

Table 2 shows the three categories of CRT response definitions. The first is based on clinical measures (patient symptoms and functional assessment). New York Heart Association class and quality of life measurements, in addition to the 6-minute walk test, exercise duration, and metabolic exercise tests, are typical clinical measures. The second category is based on LV reverse remodeling assessment. This can be performed either in the acute stage during CRT implantation and is assessed by hemodynamic parameters such as CO, or in the chronic stage assessed by an increase in LVEF or a decrease in LV end-systolic/diastolic volumes and MR. The final category includes outcome measures assessment. The measures are reductions in HF hospitalization, morbidity, and all-cause mortality. These primary event-driven endpoints are used in large clinical trials to define CRT response. Secondary endpoints usually assess both cardiac function and functional status.[38]

2.3.1 Non-response on CRT

When assessing patients with implanted CRT devices with insufficient clinical response, conduct and analyze electrocardiogram (ECG) is first step to do. Perhaps for direct comparison, a basic ECG is

Table 2. Three categories of CRT response definitions.[38]

CRT RESPONSE DEFINITIONS
Clinical Measures Assessment
NYHA class & Quality of Life
6 min walk test, exercise duration, & metabolic exercise tests (CPX)
LV Reverse Remodeling Assessment
Acute: Hemodynamic parameters (C.O., LV dP/dt $_{max}$)
Chronic: Increase in LVEF, reduction in LV end systolic/ diastolic volumes & MR
Outcome Measures Assessment
Reductions in HF hospitalizations, morbidity, & all cause mortality

needed. If a basic ECG is unavailable, comparison of the sequence from electric transmission during inactive and active pacing can be compared for the acute effects of CRT, only if the patient not relies on pacemakers. The ECG with CRT pacemakers should be compared with conventional right ventricular apical pacing, in rely on pacemaker patients. Device interrogation gives a comprehensive information about the condition of a heart failure patients. Atrial, right ventricular, and LV sensing and pacing parameters must be checked. Stimulation of phrenic nerve is frequently observed in patient with CRT and some cases may be a LV lead dislocation-related.[36]

We define non-responders as CRT patients who meet one or more of the following criteria:[36]

- Their HF gets worse after they receive a CRT device
- After 6 months of having a CRT device, they have not improved in functional classification and have increased ventricular remodeling
- They initially responded to CRT but now have worsening symptoms.

Patients who is classified as 'non-responders' by these definitions should be systematically evaluated, since non-response may be due to a number of different factors. The main reasons to which most experts attribute non-response to CRT include: improper patient selection, suboptimal lead placement, and inappropriate device programming.[36]

The first step in troubleshooting a non-responder involves a clinical evaluation of the patient's status, particularly with regard to atrial fibrillation (AF), fluid volume, and cardiac ischemia. These three conditions can all have a profound effect on not only the patient's overall sense of well-being but also on how well CRT can function.[36] For prevention of non-response to cardiac resynchronization therapy and the difference between response and non-response to CRT can be seen in tables 3 and 4.

Table 3. Prevention on non-response to cardiac resynchronization therapy.[11]

Prevention of non-response to cardiac resynchronization therapy

Non-response				
Prevention		Detection	Management[a]	
Pre-implant	Thoughtful patient selection Guidelines indications	Primary diagnosis Consensus definition Response/NR	Advanced heart failure	Treatment optimization continued Advanced care measures Mechanical circulatory support Cardiac transplantation
Implant	Optimal stimulation configuration Right ventricular lead LV lead: maximum delay Multipolar LV stimulation	Multidisciplinary approach Attending staff Heart failure team Heart failure status Electrophysiologists Device interrogations Cardiac imaging	Suboptimal device programming	Device re-programming Atrioventricular/interventricular intervals Stimulation Mode Rate Output
	Device settings Nominal Automatic Individual		Lead(s) Failure Improper position	Reoperation[a] for lead(s) Revision(s) Repositioning Addition → MSP
Post-implant	Remote monitoring—optimization of care Uptitration of pharmaceuticals Non-pharmacological interventions: Education Exercise training Heart failure monitoring	Concomitant disorders Arrhythmias Atrial fibrillation Atrial tachycardia Ventricular Mitral regurgitation Myocardial ischaemia	Antiarrhythmic drugs Catheter ablation[a] Atrial fibrillation Atrioventricular node Ventricular extrasystoles Treatment of MR[a] Revascularization[a]	

[a]All interventional choices require a careful risk/benefit evaluation.

2.4 Response to Cardiac Resynchronization Therapy Measurement

2.4.1 Functional capacity and quality of life

The evaluation of various aspects of well-being, including quality of life, symptoms, and functional capacity, showing the effects consistency, better than single arbitral criteria, as the NYHA functional class. Cardiopulmonary exercise tests are beneficial pathophysiological explorations, although they require high expertise and are time-consuming, making them unsuitable neither for large clinical trials nor clinical settings.[15]

Table 4. Responder vs. non responder.[37]

Factor	*Response more likely*	*Non-response more likely*
Patient clicnical characteristics		
Cardiomyopathy	Non-ischemic	Ischemic
Sex	Female	Male
QRS duration	>150 ms	<150 ms
QRS morphology	Left bundle branch block	Right bundle branch block, intraventricular conduction delay
LV end-diastolic volume	180-240 mL	>240 mL
Ventricular dyssynchrony	Present	Not present
Scar burden	Low, not transmural	High, transmural
Right ventricular enlargement, dysfunction	Not present	Present
Device-modifiable factors		
LV lead position	Lateral, base-mid LV	Anterior or inferior septum, apex
Percentage of biventricular pacing	99-100%	<99 %, atrial fibrilation, PVCs
AV and VV optimization	Optimal	Not optimal

2.4.2 Event-based measures

The CRT response measure which covers all causes of death inevitably includes events that are not related to CRT. However, this is the least biased way to measure the effect of CRT on mortality. HF inpatient outcomes (total length of stay in the hospital for HF decompensation treatment or number of unplanned inpatients) are appropriate for monitoring the CRT effect on the status of HF, although it can be biased, notably in open-label clinical trials.[11]

2.4.3 Remodeling measurement

Echocardiographic measurement of reverse remodeling has been widely used to evaluate the response of CRT, in mechanistic studies alone or as a secondary endpoint. A notable decrease in the dimensions of the left ventricle (LV), with or without improvement in the ejection fraction (EF), reflects a positive response with a 15-25% for the LV end-systolic volume index threshold values. There is a consensus to examine reverse remodeling when the process has stabilized after 6 months of CRT. There is no correlation found between clinical responses and echocardiographic based on comparative studies.[16]

2.4.4 Composite measures

Composite endpoints are frequently applied in CRT clinical trials. It can be relied upon only when each variable has the same significance, or one component from the endpoint (usually death) prevents the achievement of other components. Composite endpoints should not be used to increase the rate of occurrence (by adding blood tests or imaging in composites for statistical purposes) and have to be meaningful clinically. Packer's clinical composite response investigates nearly all components of HF treatment therefore has the advantage of being approved among CRT trials. Included in Packer's clinical composite is patient self-assessment and classifies patients as worsening, unchanging, or improving.[17]

2.5 Predictor of CRT Response

Foresaw the patient's response to treatment is a matter of understanding the mechanisms underlying certain therapies become doubtful. For CRT this is not easy. Although CRTs should improve cardiac asynchronous at different rates: atrioventricular, interventricular and intraventricular levels, current knowledge in the effects of CRT on genomes, transcriptomes, proteomes, and metabolomes has expanded the significant action of CRT mechanism and finally factors that affect, regulate or modulate CRT response. Understanding the cellular, biological and humoral factor influence on the CRT response remains limited but supposed to grow and may take the main role shortly.[18,19]

The role of the duration of the initial QRS as a major determinant of the CRT response has become clear since the Pacing Therapy in Congestive Heart Failure (PATH-CHF) I and II study publication. Specifically, PATH-CHF II showed that in QRS Duration patients from 120 to 150ms, CRT was less effective in increasing exercise capacity, quality of life, and peak oxygen consumption. Lately, COMPANION, CARE-HF, Heart Synchronization Therapy in Heart Failure and Narrow QRS (RethinQ) Patients, MADIT-CRT, REVERSE, and the latest Resynchronization-Defibrillation Tests for Ambulatory Heart Failure (RAFT) are done in a completely consistently show that CRT is gradually less efficacious in reducing LVESV, hospitalization frequency, and mortality rates due to the shortened QRS duration. Indeed, in the stratum between 120 and 140 ms, the opportunity ratio for all causes of hospitalization or occurrence is almost 1, and no changes neither LVESV nor LVEF.[15, 20]

Correspond to recent knowledge about ventricular electromechanics, particularly right-to-left electrical and mechanical activation sequences are deleterious, the dominant sequences are found in RV or LBBB pacing.[21,23] Recently Sweeney et al found that a strong predictor of CRT response is an ECG pattern specific for LBBB.[24] This review is suitable with the latest data from RAFT and MADIT-CRT study. The advantages of CRT in a setting of LBBB-like activation patterns is parallel with observations in LBBB experimental models.[25,26] Recent journal publications show the LBBB configuration in the ECG as a better predictor rather than echocardiographic parameters for CRT response, even a combination of two best echocardiographic parameters, intended to investigate the best echocardiographic index of the dyssynchronous.[27] The data highly suggested by the MADIT-CRT and RAFT trial clinical data, which informed a higher risk of death or major arrhythmic events in CRT with RBBB patients compared with the control group (ICD only) but a marginal reduction in the number of hospitalizations.[29] Interestingly, an increased risk of hospitalization, and the risk of death which almost 2-fold higher shown in CRT patients with diffuse intraventricular conduction disorders compared to ICD patients. Hence, the QRS duration is a selection criterion (and remains in the guidelines), it appears that configuration of LBBB must be the most significant criteria, the QRS complex duration only serves to indicate the conduction disorder severity.[15]

While the index mentioned above is intended to be a positive predictor of the response to CRT, the number of scarring seems to be a predictor of non-response CRT. Quantify and analyze the location and dimension of scar tissue in which contrast-enhanced magnetic resonance imaging (MRI) might worthwhile to be an important knowl-

edge and even to prevent non-response becomes economically attractive. Nevertheless, there is a lack of well-conducted prospective randomized controlled trials for most MRI-using studies. Most of the recently available evidence in which 1 single parameter has been investigated, comes from a single central series. Considering that the lead pacing location concerning the location of the scar may be important, it may be useful to expand initiatives to combine fluoroscopy imaging with preprocedural computed tomography or MRI scanning.[15,31]

In addition to the basic criteria regarding the situation of post-CRT which are important in predicting CRT responses. The most obvious criteria are the electricity and mechanical re-synchronization that can be determined by observing the shortened QRS duration and changes in the QRS complex form (showing a combination of RV and LV derived wave activation).[27,30] The right fusion of these 2 wavefronts requires the pacing exact position to a degree toward each other (or coherence with intrinsic conduction). The role of pace placement of leads to achieve the most perfect re-synchronization still debating. Pre-clinical and clinical data are conflicting. Helm et al show that the LV lead position is not very critical in non-ischemic dog hearts.[26] On the other hand, Rademakers et al show that the LV lead position is very important to achieve a good response to CRT.[30] Pacing at the posterolateral divider accomplishes the best intense mechanical reaction to CRT showed by both PATH-CHF I and II studies.[19] Long-term follow-up data from COMPANION and MADIT-CRT clearly did not show significant differences in patient outcomes that moved back and forth at other sites of ventricular. However, Singh et al report worse CRT patients outcomes when pacing from the site of the apex; this perception is fits with the less intense hemodynamic advantage in the PATH-CHF I study. By using echocardiographic analysis, especially 2-dimensional strain analysis can also assess good re-synchronization.[32]

Decent re-synchronization matches with increasingly uniform dissemination of pinnacle strain and loss of strain of the septum bounce back, all associated with an expansion in stroke volume and LVEF. Conversely, in sufferer where the regional peak strains distribution did not become more similar after CRT, or even more uneven, resulting in an unchanging increase in LVEF and LVESV.[33]

Some sophisticated techniques of cardiovascular imaging have been proposed with commendable intentions to lower the proportion of CRT non-respondents. With all the previous reasons in mind, one might ask: is there a better way by using heart imaging techniques to improve non-responders? The answer will depend on the measurement index. As noted before, echocardiographic indices perform sub-optimal in predicting CRT responses. This may be partly because of the Doppler image usage as a method for myocard velocity measurement. Enhanced mechanical understanding can be predicted if two-dimensional strain is used.[34] Nevertheless, even a decent forecast of reaction to CRT when using mechanical dyssynchrony indices did not provided by using the myocardial deformation measurement (MRI tagging) gold standard technique.[35] Thus the biggest advantage of specular tracking is probably the chance of getting an uncoordinated index. Speck of tracking still requires some development in techniques and users are hampered to understand what data processing is done by vendor-specific software in limited possibilities.[15]

2.6 Management for non-responder patients

The main reasons for which most experts attribute non-response to CRT include: suboptimal lead placement, improper patient selection and inappropriate device programming. In reality, there is much we still have to learn about HF. Despite these limitations, there is a great deal that a systematic approach can do to convert non-responders and even enhance the degree of CRT response in patients who are already responders.[36]

2.6.1 Patient evaluation

The first step a clinical evaluation of the patient's status, particularly with regard to atrial fibrillation (AF), fluid volume and cardiac ischemia. These three conditions can all have a profound effect on not only the patient's overall sense of well-being but also on how well CRT can function.[36]

2.6.2 Device interrogation

Once the patient's overall condition is reviewed and addressed, the CRT device should be interrogated and checked. CRT devices, like any sort of cardiac rhythm management devices, require periodic follow-up assessments. However, any time a patient is not responding well to CRT, the next step is to evaluate right ventricular (RV) and LV capture and atrioventricular (AV) and VV optimization of the system.[36]

2.6.3 Dyssynchrony evaluation

CRT devices address the mechanical dyssynchrony of the heart, specifically those that prevent the LV from contracting as a unified, coherent whole and other timing factors (such as VV and AV timing; figure 1, figure 2) that prevent the heart from beating as an effective pump. Echocardiographic evaluation of mechanical dyssynchrony is still in its early stages, but already we know that a good variable to look at is 'septal to posterior wall motion delay' of the LV, interventricular mechanical delay (IVMD), etc.[36]

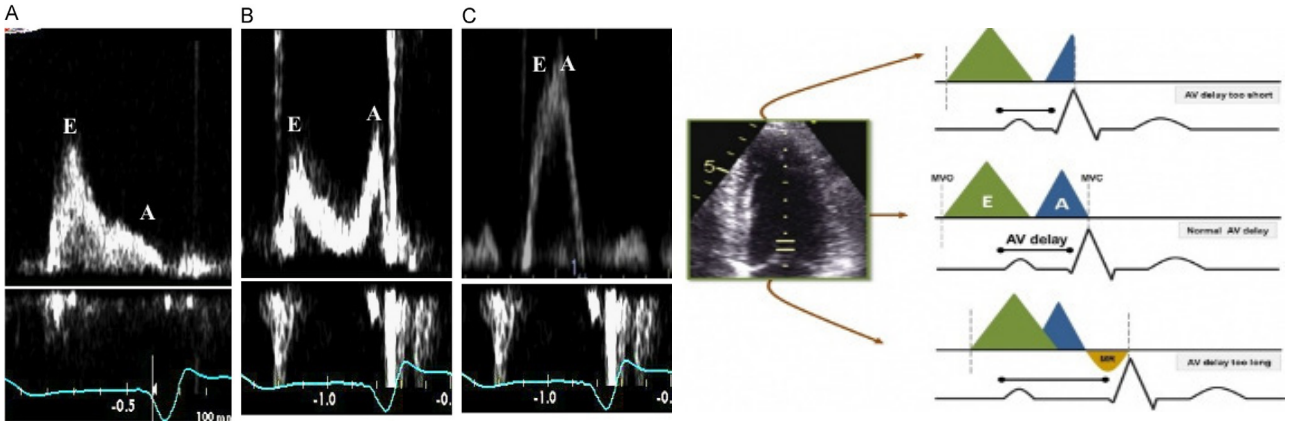
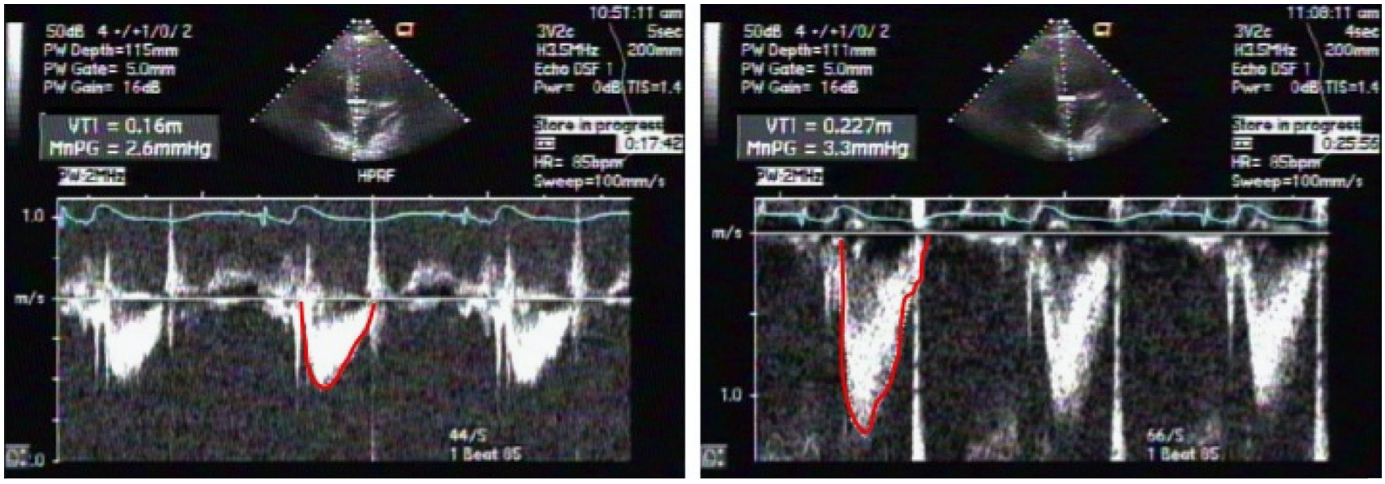


Figure 1. The iterative method. Without pacing there is fusion the E and A waves on mitral inflow. The AV delay is then gradually shortened, resulting in increased E and A wave separation until A wave truncation become apparent at a delay of 60 ms. The delay can then be prolonged in 10 ms steps to achieve maximal separation.[39]



AV delay = 80 ms
LVOT VTI = 16 cm

AV delay = 150 ms
LVOT VTI = 23 cm

Figure 2. Aortic VTI method. AV delay optimized to achieve the maximum stroke volume based on the aortic outflow tract VTI. In this case, the VTI increased from 16 to 23 cm with an increased in AV delay from 80 to150 ms. This can also be used in VV interval optimization.[39]

2.6.4 Evaluate mitral regurgitation

Mitral regurgitation (MR) occurs when blood that should be going out from the LV into the aorta ends up going backward, up toward the left atrium through the mitral valve. MR decreases cardiac output and can severely impact CRT response. In fact, persistent MR can cause non-response. Sometimes MR can be controlled or at least managed by AV delay optimization, but in other cases, valvular disease or damage makes that impossible. For some patients, mitral valve repair may be required.[36]

3. Conclusion

In the end, the CRT response is a key problem, but it has not yet been resolved. Some portion of the intricacy is identified with the way that the development of cardiovascular breakdown is as yet unusual in a solitary patient. Endeavors to improve determination of the patient to amplify the human and monetary assets use have so far fizzled. Notwithstanding, it tends to be envisioned that as opposed to distinguishing all around acknowledged cut-off qualities, hazard strata - where the incorporation of strategies for deciding LV volume, QRS length and morphology, etiology, and so forth may better give the motivation behind characterizing non-respondents. Though modalities of sophisticated cardiac imaging have been used continually to improve outcomes of patient, unfortunately, it appears that many synchronized mechanical actions suffer from difficult interpretations of complex signals and from technical limitations, which outside some highly specialized laboratories are less reproducible. Knowing the indications and possible failure of the responder is important to decrease the possibility of non-responders.

4. Declarations

4.1. Ethics Approval and Consent to participate
Not applicable.

4.2. Consent for publication
Not applicable.

4.3. Availability of data and materials
Data used in our study were presented in the main text.

4.4. Competing interests
Not applicable.

4.5. Funding source
Not applicable.

4.6. Authors contributions
Idea/concept: AMZI. Design: AMZI. Control/supervision: AR. Data collection/processing: AMZI. Extraction/Analysis/interpretation: AMZI. Literature review: AMZI. Writing the article: AMZI. Critical review: AR, HM, NK. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

4.7. Acknowledgements
We thank to Brawijaya Cardiovascular Research Center.

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