How to Define Cardiac Resynchronization Therapy Response

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ABSTRACT. Cardiac resynchronization therapy (CRT) improves quality of life, exercise capacity, and cardiac function in a significant number of patients with heart failure (HF) and left bundle branch block. CRT also reduces HF hospitalizations and overall mortality. A substantial number of patients however do not have a favorable clinical response. Evaluation of CRT non-response has been challenging as the primary mechanism for CRT improvement remains elusive. In addition, reported CRT response rates have varied significantly and are highly dependent on the criteria used to define the response. Furthermore, a disconnection exists between applying the outcome data from large clinical trials to the “real world” expectations of daily clinical practice. The ultimate goals of CRT should both met the patients’ expectations for symptomatic improvement and also improve cardiac function and/or outcomes.

KEYWORDS. Response rate, cardiac resynchronization therapy, heart failure.

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Introduction

A significant subset of patients with heart failure (HF) has cardiac dyssynchrony and delayed mechanical activation of the lateral left ventricular (LV) wall compared to the septum. Cardiac resynchronization therapy (CRT) works by improving the timing between the two segments and enhancing the overall coordination of the left ventricle. The present day approved indication for CRT is in moderate to severe HF patients with New York Heart Association class III/IV disease who are already on optimal drug therapy with LV ejection fraction <35% in sinus rhythm and QRS width >120 ms.¹

Generally speaking, CRT has been one of the most successful HF treatments to date. CRT devices have been implanted in hundreds of thousands of patients worldwide, constituting approximately 30% of symptomatic HF patients. The majority of CRT patients, approximately 70%, have experienced significant improvement in both functional capacity and survival. Unfortunately, a large percentage of patients that receive CRT do not improve clinically.

Qualitative Evaluation of Clinical Trials

The results of the first CRT trials, which included MIRACLE, MUSTIC SR, MIRACLE ICD, and CONTAK-CD,^{2–5} demonstrated that CRT improves exercise capacity in this patient population. In comparison to the control patients, the patients who received CRT in the majority of the trials had significant improvements in the 6-minute walk test and a significant improvement in peak VO₂ exchange as well.

Not only does CRT improve exercise capacity, but it can also improve cardiac function. When MIRACLE, MIRACLE ICD, and CONTAK-CD^{2,4,5} are compared, patients who received CRT in 2 of the 3 trials had a significant increase in LV ejection fraction (EF). In the MIRACLE trial, patients who received CRT also experienced a substantial reduction in mitral regurgitation (MR).

Morbidity and mortality were evaluated in multiple randomized, controlled trials.^{4–9} The pivotal Comparison of Medical Therapy and Defibrillation in Heart Failure (COMPANION) trial⁹ compared optimal medical therapy versus biventricular (BiV) pacing alone versus BiV pacing with implantable defibrillators (ICD) in 1,520 patients. The trial showed a significant reduction in death and/or any hospitalization with a higher event-free survival for both CRT pacers and CRT defibrillators. The 12-month event rate reduction was approximately 19% for both groups.

In the Cardiac Resynchronization-Heart Failure (CARE-HF) trial,⁸ all morbidity and mortality categories were significantly reduced in patients who received CRT alone without a defibrillator. The patients who received CRT had

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Figure 1: All-cause mortality data from CARE-HF comparing CRT (BiV) pacer alone to optimal medical therapy. From New England Journal of Medicine, Cleland JG, Daubert JC, Erdmann E, et al; Cardiac Resyn-chronization-Heart Failure (CARE-HF) Study Investigators, The effect of cardiac resynchronization on morbidity and mortality in heart failure, 352(15), 1544, Copyright © (2005), Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Figure 2: Cardiac resynchronization: proposed mechanisms. From *Circulation*, Yu CM, Chau E, Sanderson JE, et al, Tissue Doppler Echocardiographic Evidence of Reverse Remodeling and Improved Synchronicity by Simultaneously Delaying Regional Contraction After Biventricular Pacing Therapy in Heart Failure, 105(4), 444, Copyright © (2002), American Heart Association. Reprinted with permission from Wolters Kluwer Health, Inc.

significantly improved event-free survival compared to those who received optimal medical therapy. The two survival curves started to separate at approximately 6 months and then persisted throughout the entire duration of the trial, suggesting that the CRT response was a sustained response (**Figure 1**). In addition, the all-cause mortality included both reduction in sudden cardiac death and reduction in death due to worsening HF.

CRT Response

Mechanisms that lead to LV Reverse Remodeling

Figure 2 illustrates the theory behind cardiac resynchronization.¹⁰ CRT can improve intraventricular synchrony, atrioventricular synchrony, and interventricular synchrony.

Intraventricular synchrony. As a result of improved synchrony within the LV ventricle, systole becomes more effective, and therefore LV EF, cardiac output (CO), and other parameters of cardiac function are improved. Both LV end-systolic volume (LVESV) and MR (attributable to distortion of the mitral apparatus) are reduced. Subsequently, lowering of the left atrial (LA) pressure and LV end-diastolic volume (LVEDV) occurs.

Atrioventricular synchrony. A second mechanism is the shortening of the isovolumic contraction time (IVCT) after optimization of the atrioventricular (AV) delay. The effective diastolic filling time is increased, which in turn

raises the stroke volume. In addition, LA pressure is reduced due to decreases in presystolic MR.

Interventricular synchrony. A less important mechanism is the improvement of interventricular synchrony between the right and left ventricles. This benefit may mediate through ventricular interdependence. This results in the gain in right ventricular (RV) CO, thereby augmenting LV filling, and resulting in overall improved cardiac function. The end effect of reverse remodeling will additionally improve cardiac synchrony and decrease secondary MR, forming a positive feedback loop.

In the study by Yu et al,¹⁰ withholding BiV pacing resulted in loss of cardiac benefits. Improvements in diastolic filling time, IVCT, and myocardial performance index (MPI) were lost immediately, since they were largely dependent upon control of AV synchrony. Benefits in EF, CO, quality of life, and walking distance were gradually lost over 4 weeks, which suggests that BiV pacing may reverse LV remodeling.

Electrical versus Mechanical Dyssynchrony

Two categories of dyssynchrony have been described: electrical and mechanical. With electrical dyssynchrony, there is abnormal conduction between the atria and the ventricles, between the RV and LV, and, more importantly, within the LV. Mechanical dyssynchrony is caused by abnormal wall motion due to increased cardiac workload and stress. This involves the presence of scar and many other factors, including disruption of myocardial collagen matrix. Both of these mechanisms result in a negative impact on cardiac filling, contractility, and CO.

Table 1: Clinical studies: QRS width inclusion criteria.^{4,5,11–17}

QRS $\geq$ 120 ms	QRS $\geq$ 130 ms	QRS $\geq$ 150 ms
CONTAK-CD	MIRACLE	MUSTIC
COMPANION	MIRACLE ICD	PACMAN
PATH-CHF I & II	InSync III	CARE-HF
CARE-HF* (+ echo)		

The simplest way to measure electrical dyssynchrony is the QRS width. Table 1 presents several HF studies that demonstrated the chronic benefit of CRT and the associated QRS width criterion.^{4,5,11–17} Patients with QRS widths of 120–150 ms have also been studied.^{4,5,11–17} CARE-HF¹⁴ used echocardiographic determination to assess mechanical dyssynchrony for patients with QRS widths between 120 ms and 150 ms.

A reduction in *intraventricular* dyssynchrony has been shown to predict CRT response.¹⁸ QRS width has been shown to correlate well with *interventricular* dyssynchrony¹⁹ but unfortunately has poor accuracy for detecting *intraventricular* dyssynchrony.²⁰ As a result, it is estimated that only 70% of patients with left bundle branch block (LBBB) have echocardiographic evidence of mechanical dyssynchrony.²⁰

Yu and colleagues²¹ also demonstrated that the QRS duration may not be a reliable predictor of mechanical dyssynchrony in HF. The study assessed mechanical dyssynchrony in control patients and HF patients stratified by QRS duration. Mechanical dyssynchrony was assessed using echocardiography and was defined as the standard deviation in the time to peak systolic contraction in 12 LV segments. The study found that a majority of HF patients exhibit systolic mechanical dyssynchrony, including nearly 50% of HF patients with a “narrow” QRS (< 120 ms). Similar to previous studies²⁰ only 70% of patients with a wide QRS (> 120 ms) had mechanical dyssynchrony present.

The same group of investigators²² then examined baseline mechanical dyssynchrony to determine if it would predict CRT response. To illustrate the importance of patient selection based on mechanical synchrony, Yu and colleagues assessed baseline ventricular dyssynchrony and response to CRT as measured by reverse remodeling (reduction in LV volume) in HF patients. The study found that those HF patients with greater baseline systolic mechanical dyssynchrony exhibited greater reverse remodeling after 3 months of CRT (“responders”). The “non-responders” did not have significant baseline mechanical asynchrony and therefore did not reach the same results in reverse remodeling.

Best Measurement or Imaging Tool for Dyssynchrony

For electrical dyssynchrony, QRS width and morphology are important predictors of CRT response, particularly when QRS is > 150 ms in patients with LBBB. However, patients with right bundle branch block (RBBB) or RV paced complexes do not respond as well. Another measurement of LV electrical delay is known as QLV, which is the interval that is measured from the onset of the surface QRS to the first large positive or negative

peak of the LV electrogram. Studies have shown that QLV can be a strong predictor of CRT response.²³

For mechanical dyssynchrony, the echocardiographic measurements or tools that are presently being evaluated include LV strain and speckled tissue tracking analysis, as well as three-dimensional volumeters. In the non-echocardiographic measurements and imaging tools, cardiac MRI, CCTA, and $dP/dt_{\max}$ have also been studied. However, significant controversy exists over the most ideal measurement.

Definition of CRT response

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.²⁴ 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. However, the adoption of the results from large clinical trials in daily practice has been difficult. For example, it would be difficult to adopt the endpoint of mortality for assessing CRT response in an individual patient, as there is a lack of before-and-after comparison. As a result, recent clinical trials have switched to a clinical composite score to include clinical, remodeling, and outcome measures.

Current Issues with CRT Response

There are a significant number of current issues that exist when assessing CRT response. Firstly, the CRT response definition is highly dependent on the criteria used to define the response. Studies have suggested that the response rate will vary from 32% to 91%, depending on the criteria that were used. Thus response rates tend to be higher when clinical measures, such as subjective

Table 2: Three categories of CRT response definitions.

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

measurements, are used but are much lower when remodeling or outcome measurements are used. Also in clinical trials, there is no consensus on the optimal timeline to assess response.

Secondly, response criteria may vary greatly among investigators. For example, symptomatic improvement does not always correlate with improvement in echo or functional assessment parameters, and vice versa. Complicating factors also include the fact that acute hemodynamic or echocardiographic parameters have not been associated consistently with long-term clinical response. In addition, the best criteria to determine CRT response are unknown, and there is no true agreed surrogate for mechanical dyssynchrony.

Finally, multiple different factors between individual patients can affect the response. These factors include genetic and sex differences, stage and cause of congestive HF, LV lead location, QRS morphology and width, the presence of multiple comorbidities, LV scar in ischemic patients, and the frequency of atrial fibrillation and/or premature ventricular contractions. Device management, including optimizing AV/VV intervals and programming to ensure the greatest percentage of BiV pacing is another important consideration.

Newer trials have shown that women generally have higher rates of CRT response. Severely remodeled LV can be “beyond repair,” and these patients are less likely to respond to CRT.²⁵ Two predictors of adverse remodeling and poorer clinical outcomes are severe LV dilatation and MR.^{26,27} Non-ischemic patients generally have better outcomes compared to ischemic patients.

Regarding atrial fibrillation in HF, approximately 25% of patients with HF and up to 50% of patients with class IV HF will have atrial fibrillation. In a MADIT-CRT subgroup analysis of 213 patients who had atrial fibrillation, the investigators found that CRT had less effect on outcomes in patients with atrial fibrillation.²⁸ Patients with atrial fibrillation had poorer outcomes with higher all-cause mortality. In a meta-analysis involving 1,164 patients with CRT and atrial fibrillation, despite overall clinical improvement, the benefits appeared to be smaller compared to those who were in sinus rhythm.²⁹

Recently, the MADIT-CRT trial showed that LV lead location matters. Apical placement of the LV lead may enhance lead stability but is associated with worst outcomes.^{30,31} In the trial, distal LV lead placement increased the risk of death and/or HF hospitalization by a factor of 1.64 and increased the risk of mortality by 2.6. Therefore, LV basal pacing was better. Other trials have shown that pacing at sites of late LV activation can also improve outcomes.²³

QRS width, as discussed earlier, can be an important predictor of outcome. Patients with a wide QRS (>150 ms) have the highest likelihood of responding to CRT.^{28,32,33} In COMPANION, the primary endpoint was met only when the QRS was >148 ms. In REVERSE, the primary endpoint was met when QRS was >152 ms. In MADIT-CRT, there was a 41% reduction in HF in patients with a QRS of >150 ms. With respect to QRS width of 120–150 ms, the results of CARE-HF¹⁴ suggest that an echo dyssynchrony evaluation can be potentially

valuable. However, as previously mentioned, no reproducible single echo dyssynchrony parameter is predictive of CRT response to date.

In addition to QRS width, QRS morphology is also important. Patients with LBBB tend to respond better symptomatically than those with RV paced complexes or RBBB. Also, patients with LBBB have less chance of requiring a heart transplant or implantation of an LV system device compared to RBBB or RV paced patient populations.³⁴

Patient Evaluation: Clinical Trials versus the Real World

When comparing how patients are evaluated in clinical trials versus in the real world, several questions arise. Can large clinical trial data be applied to real world experience? For example, the older age groups are poorly represented in large CRT trials (average age 60), as opposed to in daily practice where a large percentage of patients who receive CRT devices are much older. Also, in real world experience, women are less likely to receive CRT devices compared to men, despite data that show that women tend to have a better response. Does it matter that hard endpoints like those in clinical trials are not met in daily practice? Should the goal of CRT be to reduce HF hospitalization even if the patient does not improve symptomatically? Can “no improvement” in a patient’s clinical status be good enough in a very progressive and debilitating disease? The use of event-driven measures is appropriate in large, long-term clinical trials but may not be as meaningful in the determination of an individual’s response in daily practice. In the real world, the patient’s overall sense of well-being may be a more relevant measure of CRT response.

Goals of CRT

What should be our goals for CRT? This is a difficult question to answer for many reasons. In dealing with congestive HF patients, it is difficult to predict the natural history because, many times, they follow a highly variable and progressive course. In addition, it is unknown which CRT response definition – improvement in clinical symptoms or LV reverse modeling – will result in overall improved survival. Ideally, CRT response should include both a clinical assessment and a cardiac function or outcome assessment.

Hence, reasonable goals may include, firstly, to improve the patient’s symptomatic status, such as decreasing the New York Heart Association class, and to meet the patient’s expectations of feeling better; and secondly, to attenuate pathological LV remodeling such as via a decrease in LV end systolic/diastolic volumes or increase in LV EF.

Conclusion

CRT improves quality of life, exercise capacity, and cardiac function in a significant number of patients with HF and LBBB. Furthermore, data show that it reduces HF hospitalizations and overall mortality. The mechanisms

for CRT are not known precisely, but reverse LV remodeling occurs by restoring cardiac synchrony. There is no single universally accepted surrogate for mechanical dyssynchrony. CRT response rate depends highly on the criteria used to define a response, and the criteria vary dramatically between clinical trials, so it is difficult to compare these trials with one another. A patient in one trial may be classified as a responder and that same patient may be a non-responder in another trial. CRT non-response can be attributed to multiple factors. Female gender, QRS width >150 ms, LBBB morphology, and a non-ischemic etiology demonstrate the greatest benefit to CRT. There is a significant disconnection between the clinical trial data and real world expectations, but generally speaking, in the real world, patients' overall well-being may be a more relevant measure of CRT response. Finally, the goal of CRT response should be to improve patient symptoms and reduce LV remodeling.

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