Optimal Strategies for Improving CRT Outcomes within the Real-World Practice Setting

How to Define Cardiac Resynchronization Therapy Response
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Determinants of Response to Cardiac Resynchronization Therapy
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Managing Non-responders Today and What’s on the Horizon
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Roundtable Discussion: Optimal Strategies for Improving CRT Outcomes within the Real-World Practice Setting
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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 meet the patients’ expectations for symptomatic improvement and also improve cardiac function and/or outcomes.

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

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 \( \geq 35\% \) in sinus rhythm and QRS width \( \leq 120\) 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 VO\(_2\) exchange as well.

Not only does CRT improve exercise capacity, but it can also improve cardiac function. When MIRACLE, MIRACLE ICD, and CONTAK-CD\(^2\)\(^-\)\(^5\) 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) trial\(^9\) 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...
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 Resynchronization-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.
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. 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., 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.

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.\textsuperscript{4,5,11–17} Patients with QRS widths of 120–150 ms have also been studied\textsuperscript{4,5,11–17} CARE-HF\textsuperscript{14} used echocardiographic determination to assess mechanical dyssynchrony for patients with QRS widths between 120 ms and 150 ms. A reduction in \textit{intraventricular} dyssynchrony has been shown to predict CRT response.\textsuperscript{18} QRS width has been shown to correlate well with \textit{interventricular} dyssynchrony\textsuperscript{19} but unfortunately has poor accuracy for detecting \textit{intraventricular} dyssynchrony.\textsuperscript{20} As a result, it is estimated that only 70\% of patients with left bundle branch block (LBBB) have echocardiographic evidence of mechanical dyssynchrony.\textsuperscript{20} Yu and colleagues\textsuperscript{21} 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 studies\textsuperscript{20} only 70\% of patients with a wide QRS (>120 ms) had mechanical dyssynchrony present. The same group of investigators\textsuperscript{22} 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.

\textbf{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.\textsuperscript{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 \(dP/dt_{\text{max}}\) have also been studied. However, significant controversy exists over the most ideal measurement.

\textbf{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.\textsuperscript{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.

\textbf{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

\begin{table}
\centering
\caption{Clinical studies: QRS width inclusion criteria.\textsuperscript{4,5,11–17}}
\begin{tabular}{|l|l|l|}
\hline
QRS \(\geq\) 120 ms & QRS \(\geq\) 130 ms & QRS \(\geq\) 150 ms \\
\hline
CONTAK-CD & MIRACLE & MUSTIC \\
COMPANION & MIRACLE ICD & PACMAN \\
PATH-CHF I & InSync III & CARE-HF \\
PATH-CHF II & & \\
CARE-HF* (\(+\ echo) & & \\
\hline
\end{tabular}
\end{table}
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. Two predictors of adverse remodeling and poorer clinical outcomes are severe LV dilatation and MR. 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. 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.

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. 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.

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. 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-HF suggest that an echo dysynchrony 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.

**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 remodeling – 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.

References


Determinants of Response to Cardiac Resynchronization Therapy

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ABSTRACT. Cardiac resynchronization therapy has been shown to improve the functional class and quality of life, reduce mitral regurgitation, and remodel the heart favorably, while reducing heart failure hospitalization and overall mortality in this large subgroup of heart failure (HF) patients.

KEYWORDS. Cardiac resynchronization therapy, heart failure, non-responsive.

Introduction

Cardiac resynchronization therapy (CRT) is an effective and established therapy for patients with medically refractory heart failure with left ventricular systolic dysfunction and a wide QRS complex. CRT has been shown to improve the functional class and quality of life, reduce mitral regurgitation, and remodel the heart favorably, while reducing heart failure hospitalization and overall mortality in this large subgroup of heart failure (HF) patients. Despite these beneficial effects of CRT, a significant minority (approximately 30%) of patients remains non-responsive to this therapeutic modality. Notably, there are three broad determinants of resynchronization therapy response: firstly, selecting the “appropriate” patient, secondly, implanting the left ventricular lead in the correct location, and thirdly, optimally programming the devices.

Patient selection

Echocardiography-guided cardiovascular imaging to better define mechanical dyssynchrony as a patient selection strategy has had challenges, preventing it from becoming a mainstream strategy. Imaging approaches such as magnetic resonance imaging (MRI) and computed tomography CT are evolving as tools, and their ability to provide information on cardiac function, along with the venous anatomy and scar location, may help us better select patients. At this time, we still rely on one of the most simplistic measures from the 12-lead electrocardiogram—the surface QRS signal. The QRS duration has gained the notoriety of being one of the most important criteria for identification of patients in whom ventricular asynchrony could be ameliorated by left ventricular pacing.

When looking at the impact of QRS within randomized clinical trials, it is evident that the wider the QRS the better. Patients who have a wide QRS have more mechanical dyssynchrony, and a greater extent of mechanical dyssynchrony is often times more forgiving of a suboptimal left ventricular (LV) lead position. During CRT, the right ventricular (RV) and LV leads generate two ventricular wavefronts and the benefit of CRT depends on the effective fusion of these wavefronts, synchronizing the contraction of the ventricles. Given that this pattern of electrical activation sequence in left bundle branch block (LBBB), is associated with delayed mechanical activation of the posterior basal lateral wall, targeting this region for LV pacing has been the standard approach for conventional CRT implants. In contrast to LBBB, patients with a right bundle branch block (RBBB) or non-specific intraventricular conduction delay (IVCD) have differing activation patterns and may therefore not benefit as much from CRT. Of note, there is substantial heterogeneity of activation wave fronts within bundle branch type that may be further modified by substrate phenotype including myocardial scar and inflammation. Understanding the electrical pathophysiology and rationale for CRT frames the most recent North American guidelines for CRT therapy restricting a Class I recommendation only for patients with LBBB and QRS ≥ 150.
msec. Meta-analysis of several landmark trials (COMPA-NION, CARE-HF, REVERSE, MADIT-CRT, RAFT) suggested that significant reduction of composite clinical events was present only in patients with baseline QRS ≥ 150 msec. Data from a meta-analysis in 2010, significantly influenced the European Society of Cardiology (ESC) and, subsequently, the Heart Failure Society of America (HFSA) and Heart Rhythm Society (HRS), all of whom endorsed a QRS of 150 ms to ensure response among patients with non-LBBB. As alluded to above, patients with non-LBBB have poorer outcomes largely because of variability in the activation sequence of the heart, and the conventional implant procedure may not be as effective.

Beyond QRS morphology and duration, there are several other baseline clinical features that may impact the response to CRT. In atrial fibrillation, there is loss of atrio-ventricular synchrony as well as suboptimal effective biventricular capture on account of irregular and high ventricular rates, leading to the suboptimal delivery of biventricular pacing. In a sub-analysis of patients with atrial fibrillation enrolled in the RAFT trial, it was observed that while CRT did reduce HF hospitalization (40% risk reduction), it had no influence on cardiovascular death. In addition to QRS duration and atrial fibrillation, several other factors have been shown to influence the efficacy of CRT including medical comorbidities (chronic renal insufficiency), hemodynamic pathology (pre-capillary pulmonary hypertension), and abnormalities of LV substrate (non-revascularizable coronary artery disease, myocardial scar). There has also been a suggestion that women may benefit from CRT more so than men, particularly in patients with LBBB and even at QRS duration < 150 msec. Whether these factors only satisfy the efficacy of CRT versus obviate the benefit of biventricular pacing remain to be assessed in future prospective studies.

**LV lead placement**

Response to LV lead location involves multiple variables. Covariates that can impact response to LV lead location include the substrate, ischemic or non-ischemic status, presence or absence of scar, surrounding tissue health, electrical issues, such as RV–LV fusion, depolarization wavefront, proximity of the LV lead to the Purkinje network system, orientation of the electrode, or myofibrillar pattern (Figure 1). Multiple variables can impact how the patient responds to a particular LV lead location. Thus, even if the lead is placed in the correct location, the patient may not respond because these different variables can influence the impact of pacing.

The conventional approach to implantation of the left ventricular lead is via a transvenous approach targeting the lateral or posterolateral location within a branch of the coronary sinus veins (Figure 2). This strategy takes into consideration the expected pattern of delayed electrical and mechanical activation of the lateral and posterolateral wall, particularly in patients with LBBB. Amongst the biggest challenges to appropriately targeting the left ventricular lead is the heterogeneity of coronary sinus venous anatomy.

Response to CRT is often variable even when the LV lead is placed in this optimal anatomic position, reflecting the complex interaction of myocardial substrate (e.g. scar), variability of the ventricular wavefront activation even within similar bundle branch morphologies, as well as RV pacing-induced shifts in left ventricular activation. Anatomically, placement of the LV lead can be organized along the long and short axes. Placement of the LV lead in an apical position has been shown to be associated with a worse clinical outcome. Compared to non-apical locations, the apical placement is usually neither electrically distant or adequately anatomically separated from the RV lead. Beyond anatomic targeting, individualized approaches include identification of regions of maximal electrical delay, maximal mechanical delay, or lead positions that will enhance the hemodynamics. Given that CRT is a
form of electrical therapy for patients with abnormalities of electrical conduction, it remains innate that targeting the site of latest electrical activation may yield the most favorable CRT response. While the site of latest electrical delay has been identified using various methods including three-dimensional non-contact endocardial mapping, a more practical strategy has been the use of intracardiac electrograms (EGM) to measure the delay between the surface QRS and the initial sensed intracardiac signal of the LV lead (QLV). This difference can be further corrected for baseline QRS duration to yield the LV lead electrical delay (LVLED). Lead placement at sites of increasing QLV is associated with greater rates of LV reverse remodeling and improvement in patient symptoms. Recent efforts have also demonstrated the feasibility of newer electro-anatomical mapping catheters to define sites of electrical delay.

While mechanical dyssynchrony has historically failed to predict CRT response or identify patients with narrow QRS who may benefit from CRT, newer modalities of mechanical dyssynchrony assessment (e.g. speckle tracking and cardiac MRI) are being continually evaluated and refined. In the STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) trial, a lead targeting strategy at sites of latest activation with avoidance of areas of scar was associated with significant reduction in composite outcome. Of note, exact concordance was only achieved in 30% of patients highlighting the limitations of coronary venous anatomy. To target the area of mechanical dyssynchrony, it is important to distinguish dyssynchrony from the presence or absence of scar, because oftentimes the scar itself may mimic mechanical dyssynchrony. In prospective evaluations, Bose et al. and others, and de Roest et al. have found that the likelihood of response is low when the lead is placed over a segment of scar. When the lead is placed over an ischemic segment, the response is better but is still low compared with placing the lead over an area of normal viable myocardium. These results indicate the need to individualize the LV lead implant approach in patients with ischemic cardiomyopathy. LV lead implantation at sites of scar (even in “optimal” anatomic location) has been associated with poor response to CRT; whether regular use of imaging to guide lead targeting (e.g. cardiac MRI) is advantageous requires further investigation. Finally, recent work has shown that conventional “anatomically-guided” LV lead targeting is rarely associated with optimal hemodynamic improvement at the time of implant. And although the degree of acute hemodynamic improvement has been associated with greater LV reverse remodeling, whether or not this approach is superior to anatomic, electrical, or mechanical targeting strategies needs further prospective evaluation. Patients with non-LBBB do not respond to CRT as well as those with LBBB. The reason for this is probably because of the one-size-fits-all strategy and placement of the lead along the lateral wall. The electrical activation sequence in non-LBBB may be quite different from that in LBBB. Investigators have examined electrical delay and have found that accessing the area that is most electrically delayed in non-LBBB translates into a much better outcome. This is being evaluated prospectively in the ENHANCE-CRT study to determine the outcomes of individualized targeting in patients with non-LBBB. Strategies to overcome potential limitations in lead targeting include use of multisite pacing, surgical implantation of epicardial leads, and endocardial pacing. The advent of Quadripolar leads represents a major improvement in implantation technology and has reduced the need for epicardial approaches. They allow us the opportunity to use a variety of different vectors to achieve better individualized activation of the LV within patients. Quadripolar leads allow us to place a stable LV lead, they help us avoid phrenic nerve pacing, and then perform non-apical pacing. Among the many procedural advantages, the quadripolar lead shaves time off of the procedure and at the same times provides the operator with a level of confidence that he or she will be able to implant the lead without encountering issues with phrenic nerve pacing. Data from the MORE CRT study and other studies have shown that this translates into better clinical outcomes. The results of the MORE CRT study indicate that quadripolar leads perform much better than bipolar leads. There is evidence that quadripolar leads are associated with much lower incidences of intraprocedural and immediate post-procedural adverse events, with an improvement in freedom from events, which also translates into better clinical outcomes. Some retrospective studies have examined quadripolar leads as registries and found that quadripolar leads have better clinical outcomes with reduced hospitalization for heart failure. However, prospective studies are still needed to validate these outcomes. Quadripolar leads allow us to measure the electrical delay of different electrodes, thereby allowing us to pace the heart from the most electrically delayed electrode, giving us a much larger span of the LV myocardium that can be recruited for appropriate individualized pacing. Leads that are placed in the apical region are often associated with a poor clinical outcome. Measuring the electrical delay off of each electrode in a particular quadripolar lead and selecting the electrode that is most delayed has been shown to translate into better clinical outcomes. Kendala et al. studied electrical delay within apical lead locations in 45 patients and found that those patients with longer QLV had better outcomes even though the anatomical position of the lead was in the apical region. Quadripolar leads also allow us to deliver sequential LV impulses or pulses from two or more electrodes in a sequential pattern. This can result in better activation of the LV myocardium and at the same time potentially recruit more myocardium, which in turn could result in better outcomes. Depending on how the LV lead lies across the ventricular myocardium, the sequential activation of two electrodes may vary from individual to individual and not just in a fixed conventional pattern. Studies with sequential pacing or MultiPoint Pacing (MPP) (St. Jude Medical, Sylmar, CA) have shown significant improvement in the acute hemodynamic
response measured either as LV dP/dt_{max}, LV stroke volume, or LV ejection fraction. Evidence suggests that the best MultiPoint™ Pacing (MPP) (St. Jude Medical, Sylmar, CA) is better than the best conventional pacing, again indicating that there is hope in the future for non-responders who have quadripolar leads implanted.\textsuperscript{17,18}

The MORE-CRT MPP study investigators are evaluating this concept.

Given the limitations of the transvenous route, alternative pacing approaches, such as endocardial pacing, have the potential to significantly impact the field of CRT. Endocardial pacing may offer more physiological depolarization of the ventricles that extends from endocardium to epicardium in the non-pathologic ventricle. Several techniques for endocardial pacing including trans-apical, trans-aortic, and trans-septal have been proposed. Even more recently, the WiSE-CRT (Wireless Stimulation Endocardially for CRT) study demonstrated the feasibility and safety of an endocardial LV pacing system utilizing a leadless ultrasound-based algorithm.\textsuperscript{19}

### Conclusion

There are several determinants of response for resynchronization therapy. Patient selection is important. We are still limited by our abilities with imaging, and we are still using QRS morphology. However, several imaging strategies under development will aid in patient selection and thereby enhance response. With lead implantation, anatomical targeting is not specific enough. We need to individualize our strategy through targeting electrical delay, targeting mechanical dyssynchrony, and avoiding scar and ischemia. The quadripolar lead gives us the opportunity to recruit and resynchronize more myocardium. Finally, sequential pacing is an evolving concept that hopefully will improve response.

### References

Managing Non-responders Today and What’s on the Horizon

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ABSTRACT. An important therapy in the heart failure (HF) population is cardiac resynchronization therapy (CRT). However, a significant minority gain no benefit. Prognosis in this group is generally very poor. Therefore, recognition of and remedial action (if indicated) for non-responders to CRT is of critical value. In practice, this is challenging because one or more of several factors may result in non-response. These are reviewed here and divided into pre-CRT (i.e. appropriate candidate selection), per-CRT (i.e., LV lead deployment) and post-CRT (i.e. programming and monitoring). Newer technologies that may affect degree of response are discussed.

KEYWORDS. Cardiac resynchronization therapy, non-CRT therapy, non-responsive.

Introduction
Cardiac resynchronization therapy (CRT) is an important therapy in the heart failure (HF) population. All trials have shown a durable survival benefit in the long term; however, trial enrollees have included a large population mix of men, women, patients with and without ischemia, patients with wide and narrow QRS, and those with left bundle branch block (LBBB), right bundle branch block (RBBB), or indeterminate QRS morphologies. As a surrogate for mortality, we have often used reverse remodeling as an index of CRT response. A range of effects on left ventricular (LV) function follows CRT in different individuals. Normalization of LV function improves survival to the level of the general population. An LV ejection fraction (EF) increase (which correlated with LV end systolic volume changes) of more than 20% in response to CRT improved survival more than with intermediate (10–20%) EF improvement. Non-responders—with no sign of reverse remodeling—fared poorly: 4 years after implant, there was a 50% survival rate, almost similar to those with chronic carcinoma. This is a very poor survival rate. There is a need to identify these patients early and evaluate underlying causes, correct their CRT programming if necessary, or even use non-CRT therapy for them. Therefore identifying non-responders is an important task (Figure 1).

An institutional study published in 2009 by investigators from the Cleveland Clinic identified reasons for non-response, and many of these reasons still exist today. As shown in Figure 2, suboptimal AV timing was dominant. Other reasons included arrhythmias, which correlate with a reduction in biventricular pacing burden, and decrease survival. We have advanced a great deal in our understanding of suboptimal LV lead position. Little attention is paid to mechanical dyssynchrony today, and an underlying narrow QRS < 120 ms is no longer an indication for CRT. Another reason for non-response is compliance issues. We can address these reasons for non-response categorized according to pre-CRT, peri-CRT, and post-CRT.

Pre-CRT: candidate selection
The class I recommendations for CRT now include LBBB and QRS duration > 150 ms. LBBB with a QRS duration of 120–149 ms is a class IIa indication. For those with non-LBBB patterns, there is a class IIa indication when the QRS duration > 150 ms. These guidelines were built on addressing QRS morphology without attention to QRS duration or QRS duration without attention to QRS morphology. This is an important distinction, because, for instance, we have not examined LBBB with a QRS duration of 120–149 ms in great detail or non-LBBB with varying QRS durations. Morphology as well as duration may matter in single individuals.

Study results have shown that, overall, patients who have RBBB derive no benefit from CRT. For those with non-LBBB and non-RBBB patterns (intraventricular

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conduction defects (IVCD)), CRT may even be harmful.\(^4\) Within these groups, however, there may be subsets of patients who will benefit. Among those with RBBB, LV activation delay might be masked by the surface QRS. Similarly, with IVCD, there may be coinciding right and left activation delays, but the QRS does not disclose this. Therefore we must look beyond QRS to other methodologies, such as biventricular (BiV) electrical mapping, to identify the area of late activation, direct the lead in that location and program accordingly, and potentially gain CRT benefit.

Patients with LBBB represent a population most likely to respond, but we dichotomize them by a QRS duration of 150 ms. Studies in a patient population with non-ischemic cardiomyopathy (NICM) and LBBB have shown that CRT response has high probability for those patients with QRS \(>150\) ms. The probability curve ascends from 120 ms to 150 ms in QRS duration. It peaks at approximately 150 ms, plateaus, and then dips again. However, QRS duration \(>150\) ms does not guarantee 100% response. There are still non-responders within this group of patients. Among the patient population with QRS duration \(<150\) ms, at least half of the patients have a potential for response, so we have a responsibility to identify non-responders within the LBBB population. In fact, responders with LBBB compared with non-responders displayed no difference in QRS duration, i.e. this metric was insufficient to discriminate between responders and non-responders to CRT\(^4,5\) (Figure 2).

This observation indicates that further refinements in patient selection are required. Some address refined interpretations of the 12-lead electrocardiogram (ECG). According to the Strauss criteria, rapid intrinsic conduction in V1, V2, and V3 and then broad QRS complexes, which are notched in contiguous leads V5, V6, and/or I and aVL specifies an ECG pattern within LBBB that is likely to respond to CRT. If we apply electrocardiographic imaging (ECGI) technology, which depicts electrical activation in greater detail, we find that even patients with LBBB have a wide variety of LV conduction patterns. The area of late activation can vary within the LV, and the patterns of LV activation can vary. There is evidence of patterns of LV activation that are particularly responsive to BiV pacing. This is an aspect that requires investigation in order to address non-responders.

Beyond QRS morphology and duration, other non-electrical baseline factors may affect CRT response. For instance, sex is a modulator. In a population of patients with LBBB and non-ischemic cardiomyopathy, men had a low frequency of response when QRS duration was \(<150\) ms. The response in women, on the other hand, peaked at a QRS duration of approximately 135 ms, maintained that peak, and then dipped when QRS duration exceeded 170 ms. These data from a single institution\(^5\) were

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**Figure 1:** Durability of the survival effect of cardiac resynchronization therapy by level of left ventricular functional improvement: Fate of “non-responders”. Reprinted from Heart Rhythm, 11/3, John Rickard, MD, MPH, Alan Cheng, MD, FHRS, David Spragg, MD, FHRS, et al, Durability of the survival effect of cardiac resynchronization therapy by level of left ventricular functional improvement: Fate of “nonresponders”, Pages 412-416, 2014, with permission from Elsevier.
subsequently confirmed by results from collected trial data. The data suggest that with QRS duration \(\leq 150\) ms and LBBB, CRT should be offered to female patients and a need for modification of the guidelines.

Other comorbidities include ischemia/scar and renal dysfunction. In comparison to the implantable cardioverter defibrillator population, the effect of CRT does not appear to be significantly blunted by underlying renal dysfunction. Pulmonary hypertension and remodeling (LA volume, LV volume, and mitral regurgitation) are significant contributors to CRT response. In order to assess comorbidities, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) evaluated 31 variables and identified seven that might affect future CRT response: female sex, NICM, LBBB, QRS duration \(\geq 150\) ms, prior HF hospitalization, end diastolic volume, and left atrial volume. In fact, patients with the lowest scores with these seven variables demonstrated no future CRT effect. Hence, a propensity score may be important for patient selection. One item that has not been addressed in scoring indices is the distribution and volume of scar. Greater scar in the LV correlates with poorer response, because there is less myocardium to recruit for contractile function. The relationship of scar to lead position is important. Pacing into an area of scar reduces CRT effect significantly. This is not restricted simply to ischemic cardiomyopathy; the effect also prevails among patients with NICM with mid-wall scar. Leyva et al. conducted a study on LV mid-wall fibrosis as a predictor of mortality and morbidity after CRT and found that the outcome for patients with dilated cardiomyopathy and significant scar was slightly worse than that for patients with general ischemic cardiomyopathy. The response was best for patients with no mid-wall fibrosis. Thus, the presence of scar is significant and must be integrated into candidate selection procedures.

**Peri-CRT: LV pacing lead position**

Non-apical lead placement is preferred (and is a class IIa indication in the European Society of Cardiology guidelines). However, where to site the lead non-apically remains less clear. Recommendations for lead position include avoiding posterolateral scar and targeting the site

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**Figure 2:** Probability of CRT response according to QRSd as a continuous function. Parametric model: multi-variable logistic regression shown with the corresponding 68% confidence limits. (A): Overall and (B): Gender-specific plot. Shapes were confirmed by semi-and non-parametric modeling. Reprinted from Heart Rhythm, 11/7, Niraj Varma, MA, DM, Mahesh Manne, MD, Dat Nguyen, DO, Jiayan He, ScD, Mark Niebauer, MD, PhD, Patrick Tchou, MD, Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB, Pages 1139–1147, 2014, with permission from Elsevier.
of maximal electrical delay. A qLV >95 ms seems to consistently identify patients who will respond versus those who will not be affected by CRT. Data from several studies suggest that the site of maximal mechanical delay is also a determinant of response. The morphology and duration of the paced QRS may be important. Regarding multisite and endocardial pacing strategies, there has been a significant advance in the way that we deliver leads. The multipolar lead provides not only stability and ability to program around phrenic nerve stimulation but also ability to affect future CRT response. In a comparison of distal bipole and proximal bipole, Rajamani et al. found that the proximal bipole resulted in a qLV measurement of >95 ms in >80% of patients. Having this span of electrodes and the ability to choose our pacing vectors gives us the opportunity to reach for sites of later activation. In a study of the relationship between qLV and hemodynamics, dP/dt was assessed acutely in a patient population undergoing CRT. The relationship between qLV and hemodynamics was almost linear, so the ability to reach for the latest site of electrical activation had significant effect on CRT response in terms of hemodynamics. This is dependent on the availability of coronary sinus tributaries in which to deliver the lead. When they are not available, we must resort to other means.

One option is to use more than one LV lead. Leclercq et al. conducted studies with multisite LV pacing, while Betts et al. studied LV endocardial pacing with a transventricular approach. Other previous approaches have been across the atrial septum, but implanting a lead into the LV under these conditions poses significant hazards. However, pacing the endocardium is potentially desirable because LV activation is swifter and LV activation time is reduced.

One interesting new technology involves an LV pellet, which may be delivered retrogradely via the aorta to a site in the LV. A product from EBR Systems transmits ultrasound energy to the LV, and this energy is transduced into a pacing output. In the SELECT-LV study, Reddy et al. applied this technology to conventional CRT failures (non-responders). The preliminary data showed EF improvement at 6 months with the use of this device. This is potentially a promising technique.

Figure 3: Left ventricular pacing lead position: electrical. Reprinted from Journal of Electrocardiology, 47/1, Niraj Varma, MA, DM, FRCP, Variegated left ventricular electrical activation in response to a novel quadripolar electrode: Visualization by non-invasive electrocardiographic imaging, Pages 66–74, 2014, with permission from Elsevier.
for achieving LV endocardial pacing, particularly when epicardial pacing via the coronary sinus tributaries is unavailable or ineffective. We are still confronted with the same challenges in determining which part of the LV to pace. A hemodynamics study from Derval et al. assessed endocardial pacing sites as well as epicardial pacing sites. There was a wide scatter between best and worst. However, in any single individual, stimulation from the best LV site was twice as good as pacing the worst LV site. The site was widely distributed. The authors concluded that the practice of a fixed single site in the lateral wall will not always capture the hemodynamically best site. This requires individualization. The same applies with electrical activation of the ventricle. In one study, utilization of different biventricular pacing vectors with a quadripolar lead in one individual resulted in highly variable electrical activation sequences when studied with high definition non invasive biventricular mapping (Varma17). One that resulted in the best electrical resynchronization also was associated with the narrowest QRS on the surface ECG. Thus, the availability of different pacing vectors is very useful. It can span a larger area of myocardium and give us the ability to pace more hemodynamically and electrically beneficial sites.

**Post-CRT: programming and monitoring**

The premise of CRT is that the fusion between the left and right excitation wavefronts correlates with the highest increase in LV contractility. This requires a combination of AV interval and VV interval perhaps manifest in the surface QRS. ECG fusion correlates with the best volumetric reverse modeling. QRS wideners tend to worsen. However, in trial conditions, the paced QRS does not display significant fusion in almost 50% of patients, suggesting that we do not pay enough attention to programming after implant.

With echo-guided programming, the principles are that cardiac cycle timing affects hemodynamics and E and A waves characterize LV filling, which is a critical part to LV systole. AV optimization uses coordination of the atria and ventricles, maximizes LV filling time, increases cardiac output, and facilitates ventricular synchrony. However, results with AV optimization have not shown any benefit over out-of-the-box settings. This technique may be of benefit in some individual cases of non-response. Optimization of AV intervals and VV intervals to reduce ventricular dyssynchrony has also not shown significant effect.

Recent data suggest that electrical programming might be important. We can look at the ECG and change AV and VV intervals to produce the narrowest QRS. In a single-site study from Tamborero et al., patients randomized to ECG optimization versus echo-guided optimization had better outcomes. Electrical fusion was more predictive of future CRT response. Automatic device-based programming has also been used. With the SMART AV system and the FREEDOM trial, investigators examined electrical activation based on interventricular and AV intervals assessed by the device itself. The two trials did not show benefit, possibly because they were not optimized frequently enough. During diurnal variations, AV intervals change, and perhaps the need for AV timing and VV timing also change. This is also a limitation to echo-based optimization. However, the Adaptive CRT algorithm self-regulates and reassesses timing on a minute-by-minute interval. The data from that trial have been promising. One analysis of the main trial showed that patients with a higher percentage of synchronized LV pacing in the Adaptive CRT arm had a lower rate of death and HF hospitalizations than echo-optimized patients. This suggests that there is merit in electrical optimization and also in maintaining that optimization and changing it according to needs during the day.

QRS duration may be important. With a quadripolar lead, we have the ability to simultaneously pace different vectors on this lead platform. Zanon and colleagues showed that QRS duration was significantly abbreviated by MultiPoint™ Pacing (MPP) (St. Jude Medical, Sylmar, CA) compared with standard BiV pacing. In fact, compared with BiV pacing at any LV site, MultiPoint™ Pacing (MPP) (St. Jude Medical, Sylmar, CA) yielded a small but consistent contractility decrease, which was correlated with greater QRS narrowing, again emphasizing that electrical resynchronization is an important component of increasing response. Structural heart disease may be a determinant of non-response. Mitral regurgitation is prevalent in CRT recipients. Its severity in the general HF population correlates with adverse ventricular remodeling and outcomes. Bursi et al. showed that reduction of mitral regurgitation after CRT correlated with an improvement in survival. In contrast, a deterioration in mitral regurgitation correlated with poorer survival. Auricchio et al. treated 51 severely symptomatic CRT non-responders with MitraClip (Abbott Laboratories, Abbott Park, IL). Over 12 months, 70% of patients improved and LV reverse remodeling occurred. This suggests that mitral regurgitation is a significant factor contributing to non-response that must be addressed and corrected.

Post-procedural monitoring is very important. Altman et al. showed improvement in survival with increased intensity of follow-up, multidisciplinary care, and HF evaluation. Schmidt et al. up-titrated conventional medical therapy after CRT implant and found that improved survival correlated with higher doses of neurohormonal blockers and lower diuretic doses. These results remind us of the importance of adjustment of conventional drug therapy. Regular follow-up addresses potentially asymptomatic conditions that may cause HF decompensation and deterioration in the future. We can intervene early to prevent the sequence of events that requires higher intensity of follow-up. We know that atrial fibrillation and loss of BiV pacing correlate with reduced survival, but in the current era, devices equipped with remote monitoring will inform us of these events. An implanted device will automatically link with telecommunication networks and provide notification.
of the advent of atrial fibrillation or loss of BiV pacing or PVC counts. Several other parameters are also available. This information would be automatically relayed within 24–48 h by the device, regardless of patient symptoms. In a study of patients with CRT-P (pacemaker) and CRT-D (defibrillator), survival was associated with increased adherence to remote monitoring, and survival was reduced in patients who did not maintain consistent follow-up31 (Figure 4). The INTIME randomized trial showed a similar survival benefit using remote monitoring with daily transmissions, compared to conventional care. These results point to the importance of follow-up intensity of automatic remote monitoring.

Conclusion

CRT effect and, therefore, non-response, depend on multiple factors. The magnitude of benefit depends on a variety of underlying conditions. Those with narrow QRS and non-LBBB are very unlikely to gain benefit. Atrial fibrillation may reduce positive effect. Men with ischemic cardiomyopathy have a relatively modest response. Patients with wide QRS and LBBB and women with NICM have the highest probability of response. Selection, electrical substrate, and attention to comorbidities are important. LV lead type, location, pacing effects, and programming are also important. Post-implant monitoring with early reaction to changes in either device function with reprogramming or disease status, for instance, with atrial fibrillation are very important and may affect survival. Attention to one or more of these factors may heighten CRT effect with associated survival benefit. This has not been addressed prospectively in any trials to date, but the ADVANCE CRT registry is evaluating the important patient population of non-responders to CRT.

References

Managing Non-responders


Roundtable Discussion: Optimal Strategies for Improving CRT Outcomes within the Real-World Practice Setting

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ABSTRACT. Gery Tomassoni, MD, FACC, FHRS (Lexington, KY, USA): In this roundtable discussion portion the Optimal Strategies for Improving CRT Outcomes within the Real-World Practice Setting, we are going to start with several questions. I will start the session by asking Dr. Singh and Dr. Varma how they determine if a patient responds adequately to cardiac resynchronization therapy (CRT).

KEYWORDS. Cardiac resynchronization therapy, non-responsive, response rate, heart failure.

Discussion

Gery Tomassoni, MD, FACC, FHRS (moderator):Welcome to the Roundtable on the Optimal Strategies for Improving CRT Outcomes within the Real-World Practice Setting. In this roundtable, we will discuss the strategies for improving CRT outcomes. I will start the session by asking our experts a very important question: How do you determine if patients respond adequately to cardiac resynchronization therapy (CRT)?

Jagmeet Singh, MD, DPhil: That is an interesting question, because a lot of controversy is attached to it. Most physicians look at anatomical endpoints, such as reverse remodeling, for ascertainment of response. On the other hand, some physicians say that if the patient is not feeling better, if his or her quality of life is not better, and the New York Heart Association (NYHA) class is not better, the patient is a non-responder. Response cannot be classified in a dichotomous fashion as a responder or a non-responder. One needs to look at it as a continuum where someone could be called a mild responder, a moderate responder, a high responder, or a super responder. If you maintain stability in a patient’s clinical course and he or she has not had heart failure hospitalizations, which the patient had before, there has been no change in the patient’s ejection fraction or quality of life, but at least the patient has not been hospitalized, you could call the patient a limited responder. Depending on whether the patient has improvement in his or her quality of life, in the NYHA class, without any improvement, I would call the patient a mild responder. If the patient has had a significant improvement in quality of life along with an improvement in ejection fraction, I call the patient a moderate responder. Obviously, high responders are people who almost normalize their ejection fraction. I look at it as a continuum.

Niraj Varma, MA, MD, PhD, FRCP: I agree with Dr. Singh. We treat patients to treat symptoms and also to improve their outcomes. Outcomes for the heart failure population are heart failure hospitalization and survival. If we reduce heart failure hospitalization, that is a significant response. For improved survival, that is a very significant response. If we make patients feel better, that itself is a therapeutic effect. There is a spectrum of effect, as there is with pharmacological tools. When we treat patients, some people do very well. It is usually a minority. Some people do less well and some do modestly. Still, that is an improvement. One of our roles is to improve the progress...
of patients who are doing modestly well, because there are certain techniques that we can use and that we are beginning to understand, particularly with programming. With interventions for structural heart disease, whether it is valvular regurgitation or intercurrent ischemia, there are several other things, but post-implant monitoring is very important.

**Singh:** The way we quantify response has a fair amount of subjectivity to it, when we look at quality of life, 6-minute walk test, and the like. These devices have the ability to give us a lot of diagnostic information. For example, the devices can measure physical activity, they can measure heart rate trends, and they can measure transthoracic impedance. In the future, these measures will help us define response because they will be more objective than the conventional measures that we use right now.

**Tomassoni:** It will be even more amazing if we can use the data to guide individualization of AV optimization and VV optimization to maximize the chance of responding.

**Varma:** We have that data instantly available with remote monitoring, but managing that data and assessing the signals from that data, which are important to patient intervention, is a current challenge.

**Singh:** The field is moving in the direction where a lot of the data will be processed, but they will be also used with baseline covariate data depending on sex, age, and other comorbidities. All of that will eventually get integrated, and then we can individually classify response for certain patients. Again, the fact that we classify response as a whole is really interesting. You need to classify it at the individual level, where they were and where they are now, rather than just saying where they fit into the bucket that we are using for response.

**Tomassoni:** CRT pacemakers versus CRT implantable cardioverter-defibrillators (ICDs): mortality benefit has been shown for both populations. When do you decide about putting in a pacemaker versus a pacemaker with an ICD in a CRT patient?

**Varma:** We have CRT-P and we have CRT-D. Indications for CRT-D are generally those patients with depressed ejection fraction who otherwise merit ICD implantation. For CRT-P, we have a wide variety of candidates. We have patients with depressed left ventricular (LV) function but probably above 35%. We have patients with non-ischemic cardiomyopathy perhaps related to atrial fibrillation. They are going to have AV nodal ablations or perhaps an increase in recent right ventricular pacing burden from already implanted pacemakers. These are the types of patients in whom I might consider a CRT-P. I also offer this as an option to my patients who are elderly, outlining the benefits of CRT-P versus CRT-D.

**Singh:** Dr. Varma has touched on all of the different nuances related to when you decide between a CRT-P and CRT-D. The bottom line, however, is a one-on-one discussion with patients, elucidating to them the benefits of one versus the other and the detractors of one versus the other and making them a part of that decision-making process. The bigger part of this decision usually comes in the elderly. With the elderly, there are many other measures, such as physiology or frailty index and the like, that we should be incorporating into our electrophysiological practices, but we are not there yet. Individualizing the decision with a detailed conversation with the patient is often the way I make these decisions.

**Tomassoni:** A common question that I get asked many times is regarding the time of generator change out. If patients have CRT-D devices and their ejection fraction has somewhat improved, should you downgrade them to CRT-P because of the cost-effective value of this treatment plan?

**Singh:** That is a burgeoning field of investigation right now. We published a meta-analysis on the long-term impact of an improved ejection fraction in patients who received ICDs. This was published recently in the *European Heart Journal*. We found that if they have improved above 45%, their incidences of shocks were minimal. Some data from other centers showed that if you are a super responder with complete normalization of your ejection fraction, the risk of ICD therapy is equivalent to a normal population. Again, there are nuances to this. It is not a 100% guarantee. It is an individualized decision with the patient. Rather than call it a downgrade, I call it an upgrade, because they have done so well that you can congratulate them and say, “You do not need the defibrillator anymore. You should be okay with the pacemaker.” It is an evolving question, and there will be some trials to answer this question prospectively.

**Varma:** It is a difficult choice for a patient who has been committed to a defibrillator for low ejection fraction, and then the question arises about upgrading, as you say, to a pacemaker. In our population, we looked at our group of super responders, at least those who had completely normalized the LV function, and the risk of ventricular rhythm errors was no larger than that of the general population. The survival was equivalent to that of the general population. I would look for complete normalization of the LV function and I would look for lack of ventricular arrhythmia history on the defibrillator platform before I would offer it to them.

**Tomassoni:** Do you feel that quadripolar technology should be a standard of care? Should all patients now get a quadripolar lead?

**Singh:** I would have a kneejerk reflex to that and say yes. Not only does it provide many more options for the patient, but it provides a fair amount of solace to somebody like me, who is implanting these leads. I go into the procedure comforted by the fact that I am going to come out successful and not worried about locations, stability, phrenic nerve pacing, and dislodgement because you can put the lead distally as far as you want. It does a lot of good for the patient, but it also does a lot of good for the implanting physician.

**Varma:** It is my first choice. I will use a quadripolar lead if a vessel is available to accommodate it.

**Tomassoni:** Let us talk about preprocedural evaluation of patients undergoing CRT. Should it be a standard of care that patients get some type of imaging or coronary
Singh: One area where we do perform imaging now for patient selection is when patients are referred to us as non-responders from other institutions or within our institution. We will perform echocardiographic imaging with speckle tissue tracking to see if there is any residual mechanical dyssynchrony. If there is, we will perform a CT to look at venography and to look at the coronary venous branches that are still available. Then we will decide if we are going to give the patient a second chance with a revision of the LV lead to another location. In the future, the possibility of having endocardial pacing will arise. Once we have endocardial pacing, maybe we will still use imaging, but we will use hemodynamic measures interprocedurally to help guide us also.

Tomassoni: You mentioned CRT non-responders. We know that individually there could be many different factors in a particular patient, but if there was one hard-pressed factor that you think is the most important, which one would it be?

Varma: I would say lead position plus programming. That is technically two things, but I think they are linked.

Singh: I would say lead positioning if I had to choose one. A variety of patients may be potentially non-responders, but if you could position the lead appropriately in those patients, you could have a response. The additional impact of programming compared to lead positioning is less incremental.

Varma: Let me challenge you on that. In certain subgroups, the apex might still be viable, but let us say we avoid the LV apex as a lead position. If we remove the septal segments, you have more than 10 segments that have equal probability of producing the best hemodynamic response.

Singh: That is why I think lead positioning is important, because you are not looking at the apex. What you are trying to do is find the area that has the maximal electrical delay where you potentially have response. Even if it is a non-left bundle or a left bundle, you do not just put it anywhere on the lateral wall and avoid the apex, but you try one or two or three branches. Get the segment of maximal electrical delay, avoid the apex, but use a segment that you think would be most individualized in that particular patient. If you get that segment and you have a significant delay, then the incremental value of AV optimization is relatively less, as it would be in a suboptimal location. I would still hang my hat on lead positioning.

Varma: There is another factor, which is the effect of LV pacing. You can pace from the site of maximal delay, but if your wavefront is jailed, then it is programming.

Tomassoni: If there is one technology right now or in the near future to help with non-responders, what do you see that to be? Is MultiPoint™ Pacing (MPP) (St. Jude Medical, Sylmar, CA) one of those possibilities, or should we be looking for something else in the next few years that may revolutionize non-responder rates?

Singh: I think it will be a combination of multisite/ MultiPoint™ Pacing (MPP) (St. Jude Medical, Sylmar, CA). Obviously, we are going to have to understand the electrical activation sequence and the mechanical contractility of the heart a little better. A combination of multiple electrodes or multiple sites and integrating the electrical activation sequence in a better individualized fashion may be something that is really exciting. Also, LV endocardial pacing—not initially for conventional patients, but for non-responders—may be a good strategy for the future.

Varma: I think that understanding electrical activation matters if we improve our candidate selection. We can
have women with non-ischemic cardiomyopathy and wide left bundle branch block. A proportion of those patients do not respond, and we have to understand why. I think that effect is magnified in other groups, particularly as the QRS morphology becomes less specific for left bundle branch block. A vital ingredient here is the effect of LV pacing, and I think we need a mechanism. I completely agree with your point of using pacing sites within the LV that produce the best electrical effect coupled to the best hemodynamic effect, and we have not really assessed that yet. That might involve multielectrode pacing, simultaneous electrode pacing, or endocardial pacing, and I think one of the promises of endocardial pacing to improve response rates is the fact that electrical activation is accelerated across the endocardium as a faster activation time. That really shows that the electrical activation in response to pacing is a vital ingredient to CRT effect.

Singh: One more therapy that I think is exciting is His bundle pacing. There is a small subset of patients who may have a borderline ejection fraction but have AV conduction block and require pacemakers. Rather than going down the CRT path immediately, one might think about His bundle pacing in the near future. This is an evolving strategy getting a fair amount of traction.