Cardiac resynchronization therapy (CRT) has gained widespread acceptance as a safe and effective therapeutic strategy for congestive heart failure (CHF) refractory to optimal medical therapy. The use of implantable devices has substantially altered the natural history of systolic heart failure. These devices exert their physiological impact through ventricular remodeling, associated with a reduction in left ventricular (LV) volumes and an improvement in ejection fraction (EF). Several prospective randomized studies have shown that this in turn translates into long-term clinical benefits such as improved quality of life, increased functional capacity, and reduction in hospitalization for heart failure and overall mortality. Despite these obvious benefits, there remain more than a few unresolved concerns, the most important being that up to one-third of patients treated with CRT do not derive any detectable benefit. There are several determinants of successful delivery and response to CRT, including selecting the appropriate patient, patient-specific optimal LV pacing lead placement, and appropriate post-implant device care and follow-up. This article highlights the importance of collectively working on all of these aspects of CRT to enhance and maximize response.

**Patient Selection**

**Surface Electrocardiogram and Mechanical Dyssynchrony**

After meeting the criteria of compromised LV function and medically refractory heart failure (NYHA >3), patient selection is still driven by the presence of a wide QRS on the surface electrocardiogram (ECG). It is noteworthy that ECG evidence of an intra-ventricular conduction defect, although a surrogate for ventricular dyssynchrony, is not predictive of acute and long-term response to CRT. The imprecision in the ability of surface QRS to predict response is explained by the complexity and multiple levels of electrical and mechanical dyssynchrony in the myopathic heart. This dyssynchrony can exist at numerous levels and can be inter-atrial, atrio-ventricular, inter-ventricular, intra-ventricular, or intramural. Most studies have emphasized the importance of intra-
ventricular dyssynchrony as the main contributing factor to progressive heart failure and determination of CRT response.\(^7\)

Although a QRS width $>$120ms is an accepted selection criterion, there is evidence that the degree of change in the QRS duration (post-pacing) does not predict outcome from CRT.\(^6\) This perhaps relates to the fact that a summated signal of RV endocardial and LV epicardial pacing does not correlate with the extent of change in mechanical dyssynchrony or global systolic function. The value of the surface QRS signal is further reduced by the fact that there are patients with a wide QRS duration who have minimal mechanical dyssynchrony, while there are those with a narrow QRS and significant mechanical dyssynchrony.

To further complicate matters, we now know that there is considerable inconsistency in the clinical response between patients with left bundle branch block (LBBB) and non-LBBB morphology. Characteristically, LBBB is linked with a U-shaped activation pattern that courses the apex with delayed activation of the lateral and postero-lateral portion of the LV.\(^2\) This spread of electrical activity parallels the mechanical activation, and constitutes the basic reasoning behind the conventional LV lead implantation strategy of targeting the lateral wall. Even in a pure LBBB, there remains a high level of heterogeneity in the LV activation pattern, accompanied by a wide variance in the line of functional block.\(^8\) Recent work has suggested that within patients with a non-LBBB morphology, a non-specific intra-ventricular conduction defect (IVCD) subset has a poorer outcome, while those with right bundle branch block (RBBB) fare even worse.\(^11\) Also noteworthy is that patients with an RBBB have a 3.5-fold higher risk for death compared with those with an LBBB. Several explanations for a worse outcome in RBBB patients have been touted and include ventricular dysynchrony patterns not favorable for CRT, concomitant RV dysfunction, and more extensive conduction disease.

From the activation sequence perspective, it can be speculated that the reduced response to CRT in this patient group is consequent to an unchanged lead implantation strategy (i.e. targeting the lateral wall) despite the altered depolarization wavefront characteristics in this group. In fact, it is unclear whether an LV lead is really mandatory to accomplish CRT functional gain or if an adequately timed pacing impulse from an RV lead may be adequate. Recent work suggests that although only one-quarter of patients with RBBB may have LV conduction delays comparable to LBBB, nearly 50% have some delay, which may be amenable to resynchronization.\(^12\)

**Imaging**

Simplistic approaches examining the QRS axis, morphology, and duration from the surface ECG have not been able to forecast the electrical activation pattern of the ventricles. Hence, a variety of echocardiographic measures have surfaced to improve our understanding of the anatomical and functional aspects of the cardiac substrate. M-mode, 2DE, 3DE tissue Doppler imaging (TDI) provides a better understanding of the level of baseline dyssynchrony, acute response, and evidence of favorable remodeling to CRT. Despite being recently maligned via a couple of negative studies (RethinQ, and Predictors of Response to CRT [PROSPECT]), ultrasound TDI still remains one of the most convenient and better understood tools to measure dyssynchrony.\(^13,15\) There remains, however, a lack of standardization in accepted measures, as well as several limitations to this technology. TDI is still predominantly a 2D technique and the need for high frame rates required by this technique limits resolution and image quality. Also, on account of its angle dependence, TDI allows only specific views of the cardiac anatomy. Strain-rate imaging constitutes one of the newer echocardiographic imaging strategies, and is being prospectively evaluated as part of several ongoing studies. Also, of late, realtime 3D ultrasound, which allows for simultaneous imaging of all of the cardiac segments in a cardiac cycle with new segmental wall volume techniques, may provide a better understanding of the extent of cardiac dyssynchrony during the same cardiac cycle (see Figure 1).

Since most of the imaging modalities provide complementary information regarding cardiac structure (e.g. fluoroscopy for coronary venous anatomy) and function (e.g. echocardiography for mechanical dyssynchrony), combining some of these technologies may help improve the diagnosis and facilitate the planning of treatment and delivery of pacing therapy in patients receiving CRT (see Figure 2).\(^15,16\) Data from small retrospective studies have shown that pacing over the site with maximal discordance and avoiding a region of scar may result in a better outcome.\(^17,18\) Current use of intra-procedural echo to demonstrate the most delayed segment to guide LV lead placement is cumbersome and technically challenging. Hence, pre-procedural evaluation of mechanical dyssynchrony and intra-procedural integration with venous mapping may be a useful strategy, but still needs to be effectively developed and tested prospectively.\(^15\)

Single imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have the potential to provide both anatomical and functional information, thereby obviating the need for image-integration strategies. Multidetector CT (MDCT) has the potential to provide important information pertinent to: the coronary venous anatomy, i.e. distribution of tributaries, patency, and luminal size of the coronary veins; LV contractile function; localization of scar; mechanical dyssynchrony; and integrated information regarding the relationship of the venous branch with the segment of dyssynchrony and/or scar.\(^19,20\) MRI is actively being evaluated for its ability to more precisely quantify dyssynchrony and better select patients. Currently, work at the MRI level is also focusing on the development of novel methods to characterize myocardial fiber architecture and ultrastructure and 3D
imaging of myocardial strain. MRI, however, remains a logistically challenging proposition in this population of sick patients, many of whom may have pre-existing implanted devices.

Beyond QRS duration and imaging-based demonstration of anatomical and functional characteristics, there are many clinical characteristics that could affect ventricular remodeling and clinical outcome. Although delving into each of these is beyond the scope of this article, it is important to recognize that patients with RV dysfunction, end-stage renal disease, high scar burden, and markedly enlarged hearts are liable to have a diminished response to CRT.

**Implantation Strategies**

So far, the approach for lead positioning has been rather simplistic and has been typically directed at placement of the lead along the lateral wall of the LV. Data from small retrospective studies have shown that pacing over the site with maximal discordance may have better reverse remodeling and an improved clinical outcome. In all of these studies, the assessment of the lead–segment relationship was a retrospective assumption without true image integration. Nevertheless, these and other studies have shown that reversal of mechanical dyssynchrony and improved remodeling of the heart is the primary underlying mechanism for improvement with CRT.

The importance of venous angiography during LV lead implantation cannot be overemphasized. As our understanding of CRT has evolved, it has become clear that a venous map helps us individualize our approach by selecting the most suitable lead for the appropriate branch anatomy (see Figure 3). Also important is the need for a segmental classification of the coronary veins and tributaries in relation to the LV wall in a manner comparable to that of echocardiography and LV angiography. This is particularly important when targeted LV lead placement is attempted. Transvenous LV lead placement is dependent on the availability of a vein and, due to the variable coronary venous anatomy, there may not always be a suitable ‘major’ vein in the region of interest. This complex interaction between the unpredictable LV activation pattern, the unsystematic selection of the pacing site (dependent on the presence of a suitable venous branch), and RV pacing-induced shifts in the electrical and mechanical activation pattern of the LV could be a potential explanation for the high percentage of non-responders to CRT (even with anatomically optimal LV lead positions). Also often overlooked are intra-procedural aspects of lead placement, such as the anatomical lead position, proximity to scar tissue, concordance with the segment of mechanical dyssynchrony, impact on mitral regurgitation, and relationship with intrinsic ventricular activation, which can play an important role in determining the response to CRT.

**Ventricular Pacing Site**

CRT improves LV synchrony via stimulation of the late-activated regions of the LV. Several reports have indicated that LV lead placement at an optimal anatomical pacing site (usually defined as the lateral and postero-lateral LV wall) is a critical determinant of short-term outcome. However, lack of a favorable acute hemodynamic response and the absence of improvement in symptom class in nearly one-third of the patients receiving CRT suggest limitations in our current approach to pacing-site selection. Selecting the ‘appropriate’ patient for CRT but stimulating an ‘inappropriate’ site remains an important cause of this non-responsiveness to CRT. Inter-patient variability in the LV electrical activation sequence, inconsistency of the coronary venous anatomy, and the need for acceptable pacing parameters may preclude the attainment of an ‘optimal’ LV pacing site in some patients. However,
there is evidence that the electrical activation pattern is different among patients with similar left bundle branch configurations, suggesting that an optimal anatomical site may not be reflective of the site with maximal electrical delay or mechanical dysynchrony. Our recent work has shown that pacing from a site with more delayed electrical activation, as assessed by an LV lead electrical delay greater than half the width of the baseline QRS (LVLED >50%), is associated with a beneficial acute hemodynamic response (measured as percentage change in dP/dt) and an improved long-term outcome (see Figure 4). Recent work has also suggested that site-specific pacing over the segments with dyssynchrony may be associated with a better clinical outcome. Another important aspect of LV lead placement relates to physical separation between the two pacing electrodes. However, there is still no conclusive study delineating whether the best lead implantation approach is targeting the most electrically delayed segment, lead placement over the most mechanically delayed segment, anatomical lead positioning in the lateral and postero-lateral segment, or maximizing physical separation between the RV and LV leads.

Similar to the native LBBB, RV pacing causes abnormal activation and consequently dyssynchronous contraction of the LV. Upgrading chronically RV-paced cardiomyopathy patients (who meet all other criteria for CRT) can improve heart failure by virtue of reduction in the variation of LV myocardial segmental contractility, reduction in isovolumic contraction time, improved myocardial performance index, and improved global systolic function. Another less well understood entity is the impact of RV pacing lead location on the LV depolarization wavefront and its consequent impact on resynchronization. Previous work has demonstrated that shifting the RV pacing lead can alter the LV activation sequence. An interesting question that could benefit from further investigation is the interaction between the RV and LV pacing lead location and its impact on response. Another issue that needs to be examined is the effect of scar on ventricular remodeling, as determined by the proximity of the pacing lead to the akinetic (scar) segment.

Follow-up Strategies

A new genre of ambulatory heart failure patients with implanted devices has resulted from the high prevalence of heart failure and increasing patient population eligible for device therapy. This is a frail group of patients needing care from their primary cardiologist, electrophysiologist, and heart failure specialist, often with additional input from an imaging (echocardiography) specialist (see Figure 5). Most centers lack a form of structured cross-talk between the cardiac sub-specialties and often several weeks may pass between individual sub-specialty evaluations, resulting in disjointed and often sub-optimal medical care. Current post-device-implant care is deficient on many fronts, namely consideration of device diagnostic information and utilization of such data to titrate medications, enhance device response in patients, and, more importantly, enable early identification and treatment of non-responders. There is a certain level of reticence when it comes to proactively optimizing the atrio-ventricular and inter-ventricular timings of these devices to maximize the stroke volume. Several studies have now demonstrated that device optimization facilitates functional improvement and increases the extent of reverse remodeling.

Non-responsive patients usually come to attention via a heart failure exacerbation or a hospitalization, and one of the goals of an integrated healthcare delivery program is to detect problems early, with proactive modification of the drug regimen or device settings to prevent acute disease decompensation. Having all the disciplines work together can facilitate better patient selection, CRT device optimization, and careful titration of medical therapy in the post-implantation period. A multidisciplinary clinic provides an ideal structure for consultation between different specialties to allow these devices to be used more efficiently in the care of these patients. Although it appears intuitive that this multispecialty model would translate into better patient care, the impact of such integrated services still needs to be prospectively assessed.

CRT devices record and provide detailed information pertinent to patient activity, heart rate, autonomic activity, and transthoracic impedance, and in the near future they will also provide realtime hemodynamic data. The recent advent of remote monitoring of these devices has enabled the realtime automatic transmission of ambulatory information regarding heart rate, physical activity, development of incipient pulmonary edema (transthoracic impedance measure), etc., via the Internet. Although this may result in a risk of information overload, it provides the opportunity to enhance the quality of patient care and identify non-responders well before they actually decompensate. Also, ongoing work to enhance sensor technology has enabled over-the-web transmission of other
important parameters such as blood pressure, weight, oxygen saturations, etc. Web-based monitoring of these patients and their devices provides the option for the different sub-specialists to share patient data and individualize treatment, and consequently reduce hospitalizations.

**Conclusion**

Although CRT has had a large impact on the field of heart failure, its complete potential has not been realized. Over the next few years, our understanding of ventricular mechanical dyssynchrony along with substrate- and pacing-site-specific response will improve, enabling wider application of multistate pacing of the ventricle(s). There is a clear benefit of device therapy in the symptomatic patient refractory to conventional medical therapy, and recent evidence from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) and Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE-HF) studies suggests the possibility of its role expanding to include well-controlled and mildly symptomatic heart failure patients (NYHA class I and II).

As the population eligible for device therapy rapidly expands, the need to be more cognizant of its cost-effectiveness and to refine the selection criteria will become more important. In order to maximize the level of response derived from device therapy, we have to make certain that we not only select the appropriate patient but also thoughtfully implant the pacing leads and ensure that the patients receive co-ordinated multispecialty post-implant care.

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