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Pre-Implant Assessment For Optimal LV Lead Placement In CRT: ECG, ECHO, or MRI?

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Abstract

Cardiac resynchronization therapy (CRT) improves cardiac function in many patients with ventricular dyssynchrony. The optimal use of imaging for pre-implantation assessment remains a subject of debate. Here, we review the literature to date on the utility of echocardiography and cardiac MR, as well as conventional ECG, in choosing the best site for LV lead implantation. Prior to the use of imaging for pre-implantation evaluation, LV leads were placed empirically, based on average responses from population-level studies. Subsequently, patient-specific approaches have been used to maximize response. Both echocardiography and cardiac MR allow determination of areas of latest mechanical activation. Some studies have found improved response when pacing is applied at or near the site of latest mechanical activation. Similarly, both echocardiography and cardiac MR provide information about the location of any myocardial scar, which should be avoided when placing the LV lead due to variable conduction and high capture thresholds. Alternative approaches include targeting the region of latest electrical activation via measurement of the QLV interval and methods based on intraoperative hemodynamic measurements. Each of these modalities offers complementary insights into LV lead placement, so future directions include multimodality pre-implantation evaluation, studies of which are ongoing. Emerging technologies such as leadless implantable pacemakers may free implanting electrophysiologists from the constraints of the coronary sinus, making this information more useful and making non-response to CRT increasingly rare.

Introduction

Ventricular dyssynchrony is a primary electrical disease caused by deficits in infrahisian conduction that results in mechanically inefficient cardiac pump function. Ventricular dyssynchrony, typically manifest in the form of left bundle branch block, affects roughly one-third of patients with symptomatic heart failure.[1] The consequences of such include depressed ejection fraction, decreased exercise tolerance, and increased mortality.[2, 3] In patients with LBBB, activation of the left ventricular lateral wall is delayed. The result is that early in systole, unopposed ventricular septal contraction generates stretch of the still quiescent lateral wall; in late systole, delayed lateral wall contraction occurs against an already pressurized blood pool, resulting in increased wall stress, poor mechanical function, and even aberrant myocardial expression of a variety of proteins including mediators of stress response, calcium handling, and myocyte coupling.[4–6]

Cardiac resynchronization therapy (CRT) is a pacing-based approach to treat patients with ventricular dyssynchrony. Pacing of the late-activated lateral LV to resynchronize ventricular activation has been demonstrated to improve both echocardiographic parameters (LVEF, LVESV, LA volume) and physiologic measurements (max dP/dT) of left ventricular function, as well as clinical outcomes, including NYHA class, six-minute walk time, frequency of arrhythmias, quality of life, hospitalizations for decompensated heart failure, and mortality.[7–13] CRT has proven to reduce morbidity and mortality in patients with severe symptomatic CHF and LBBB, and in patients with more mild CHF symptoms.[8, 14–16]

However, even in trials with appropriate patient selection (LBBB, systolic dysfunction), there continues to be a substantial minority of patients who derive limited benefit from CRT--the so-called non-responders. Depending on the criteria used to determine response, whether echocardiographic, clinical, or biochemical, between 20% and 50% of patients are non-responders.[17] Reasons for non-response may be multifactorial, and likely arise in part from interplay between the site of pacing and the particular substrate (i.e. scar burden, patterns of conduction) being paced.

There are two approaches to CRT lead placement--anatomic and patient-specific. Early studies investigated which anatomic sites produced the best response on a population level. Briefly, they found that basal and lateral sites produced better responses than apical and septal sites.[18] Subsequently, newer studies have incorporated patient-level data, usually imaging, in seeking to find the best sites for the patient at hand. Imaging modalities are used to avoid regions of scar and to target either regions of latest electrical activation or regions of latest mechanical activation. The purpose of this review is to consider different imaging modalities – ECG, echo, and MRI – and their role

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(if any) in the delivery of CRT.

Empiric Lead Placement

Early studies in CRT efficacy as a function of pacing site found that left lateral and posterolateral pacing resulted in greater improvement in pump function than anterior or septal pacing.[10, 18] For years, then, operators implanting LV pacing leads targeted lateral and posterolateral CS tributaries. More recently, a number of studies have suggested that there may be significant patient heterogeneity in optimal pacing sites. Bordachar and colleagues found, in a small series of patients with non-ischemic CMP, that there were frequently patients with optimal LV function attained by pacing non-traditional sites.[19] In a complimentary series of patients with ischemic CMP, Spragg and colleagues found similar results – namely, that there was significant inter-patient heterogeneity in terms of LV pacing sites that yielded optimal LV pump function.[20] Finally, in a larger series of patients receiving CRT for more mild CHF symptoms, Singh and colleagues found that clinical response among patients with anterior, lateral, or posterolateral sites was similar.[21] Apical pacing, though, clearly predicted worse outcomes in this large series of patients.

Based on these trials, many practitioners continue to target lateral and posterolateral pacing sites, delivering therapy that, at the population level, leads to good results in the majority of patients. However, persistent issues with non-response, as well as the desire to maximize response in an individual patient, has led to a broad area of investigation into targeted, patient-specific LV lead placement. Typically that tailored therapy is based on imaging of scar, of mechanical activation timing, and (during implant procedures) of local electrical activation timing as well.

Pre-Implantation Evaluation Modalities

The three main modalities employed in pre-implantation evaluation to guide placement of the coronary sinus lead are ECG (including both twelve-lead and more extensive body-surface mapping), echocardiography, and MRI. In general, the response to CRT is greatest when biventricular pacing serves to make the left ventricular contraction as synchronous as possible. The two criteria for pacing sites that might be predicted to optimize CRT response include (1) pacing at live, non-scarred, myocardium, and (2) pacing at the area of most delayed mechanical contraction or electrical activation. Echocardiography and MRI elucidate both regions of latest mechanical activation and areas of scarred, non-contractile myocardium. In contrast, ECG excels in determining the regions of latest electrical activation; it has some abilities to localize scar, but generally with insufficient spatial resolution to guide lead placement.

Eligibility For CRT And Non-Response

The use of advanced pre-implantation evaluation modalities to optimize LV lead placement assumes appropriate initial patient selection for CRT. While novel screening measures for CRT candidacy have been explored, the simple surface ECG remains the most commonly used and reliable tool for determining likelihood of CRT response. In patients with severe CHF symptoms, LBBB morphology and QRS width > 150ms have been shown to predict greatest likelihood of CRT benefit. Narrower QRS width and/or non-LBBB morphology, while not prohibitive, have been associated with lower response rates. In patients with modest heart failure symptoms, non-LBBB morphology has been shown to predict minimal CRT response, and potentially even harm from LV pacing. Current guidelines emphasize the results of these studies in determining eligibility for CRT (see Figure 1, adopted from 2013 Appropriate Use Criteria).[22]

Avoiding Scar

Patients with ischemic cardiomyopathy, by definition, have fibrosis and scarring of ventricular myocardium. Patients with non-ischemic cardiomyopathy, too, have been shown to have significant burdens of ventricular scarring.[23] In all patients undergoing CRT implant, then, there is the potential for complex patterns of scar generating lines of conduction block, unpredictable patterns of wave front propagation from LV pacing sites, and the possibility of diminished response to CRT. Some studies have shown that global scar burden predicts a worse outcome than that accounted for by the decreased LVEF alone, suggesting the electrical abnormalities in scarred myocardium pose an additional burden.[24, 25] In addition, several studies have demonstrated that pacing near scar is associated with worse outcomes[26] presumably secondary to the unpredictable patterns of regional conduction, variable latency, and high thresholds that are characteristic of regions of myocardial scar.

Both echocardiography and MRI help localize regions of scar so that leads can be placed over healthy myocardium. On echocardiography, the ventricular wall must thicken by at least 10% with electrical activation to provide evidence of functioning myocardium. Several studies have found that this degree of thickening on echo is well-correlated with uptake on technetium scan, implying that the tissue at hand is metabolically active and not scar. On MRI, myocardial scar burden can be quantified and compared between potential target regions using late gadolinium enhancement. The fact that echocardiography and MRI are able to localize myocardial scar is an important point that argues for inclusion of at least one of these imaging modalities in preoperative planning, as neither the surface EKG nor intraoperative capture threshold measurements are sufficiently accurate at localizing myocardial scar and avoiding the problems that follow pacing in adjacent regions.

Some studies have shown convincing evidence that avoiding regions of scar is an important component of optimizing CRT response.[27, 28] While the major focus of these trials was to target latest mechanically activated regions of myocardium, as assessed by echocardiography, LV lead placement was also steered away from regions of myocardial scarring. The suggestive results of those trials (described in more detail below) may be in part due to avoidance of pacing in regions of ventricular scar.

Strategies For Pacing At The Site Of Latest Mechanical Activation

Ventricular dyssynchrony represents the variability in time of contraction between the different regions of the ventricle. Intuitively, pacing at the site of latest mechanical activation is appealing as a strategy for optimizing CRT response. There have been a number of efforts to use either echo or MRI-based ventricular imaging protocols to guide CRT therapy, with variable results.

Initially, studies utilizing tissue Doppler echocardiography to guide lead placement were disappointing, including the PROSPECT trial.[29] Although utilizing echocardiography to predict response to CRT is intuitively appealing, since the correction of dyssynchrony is the mechanism by which CRT benefits patients, investigators found that echocardiographic measures of dyssynchrony added little predictive power in patients who met standard indications for CRT. Several prospective, randomized studies have since demonstrated clinical

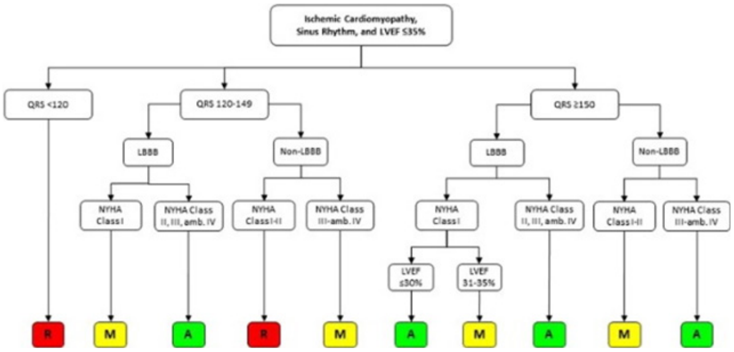

Figure:1 Appropriate use criteria for CRT in patients with ischemic cardiomyopathy (adopted from Reference 22). A = appropriate; M = may be appropriate; R = rarely appropriate.

improvement when echocardiographic measures of latest ventricular activation as seen through speckle-tracking are used to guide CS lead placement. The TARGET study randomized patients to either lead placement informed by speckle-tracking echocardiographic measures of latest ventricular activation (latest site of peak contraction with an amplitude of greater than 10%, i.e. latest-contracting myocardium that was not scar) versus routine, non-guided lead placement.[27] The result was clinically significant, with 70% of patients in the echo-guided arm meeting the primary endpoint of at least 15% reduction in left ventricular end-systolic volume (LVESV), in contrast to the 55% of patients achieving this in the control arm. Patients who underwent echo-guided lead placement also had fewer heart failure-related hospitalizations and decreased all-cause mortality. The STARTER trial was similarly designed and yielded concordant results, demonstrating decreased combined all-cause mortality and hospitalizations for heart failure among patients in the echo-guided arm.[28] See Figure 2 for an example of speckle tracking to identify site(s) of latest activation, as performed in the STARTER trial.[28] It should be noted that in both trials, the combined endpoint of death and CHF hospitalization (a secondary endpoint in TARGET and the primary endpoint in STARTER) were reduced, but that the reduction was driven entirely be lowering of CHF events rather than mortality. These studies, while promising, were limited in terms of sample size, number of participating centers, and need to be validated by broader investigations.

MRI has also been used to localize the regions of latest mechanical activation and guide LV lead placement. Compared to echocardiography-based lead placement studies, MRI is not as well-developed, but it remains promising.[30] Feasibility studies have proven that MRI-guided lead placement is possible,[31, 32] but randomized clinical trials demonstrating improved outcomes using this modality in contrast to empiric lead placement or echocardiography-based lead placement are still in progress.[33] MRI has also been used to quantify dyssynchrony and studies have shown that the degree of intraventricular dyssynchrony, as measured by the time-delay between earliest and latest regions of radial mechanical activation, has value as a predictor of morbidity and mortality, even with CRT.[34] One interesting finding of this study is that there appears to be an upper limit of mechanical dyssynchrony that can be corrected by CRT--patients with the highest ventricular dyssynchrony not only fared the worst, but also experienced no increase in LVEF with CRT. Prior investigators have come to similar conclusions.[35] The characteristics of the dyssynchrony, including the regional circumferential strain, can predict improvements in functional class with CRT, so MRI may have some added value in predicting outcomes over and above any utility in guiding lead placement.[36]

It should be noted, however, that although speckle-tracking echocardiography and MRI can be used to determine the site of latest ventricular mechanical contraction, implanting electrophysiologists are constrained by the distribution of the CS tributaries. Consequently, knowing the region of latest mechanical activation is necessary but not sufficient for pacing near sites of greatest mechanical delay. In fact, subsequent analysis of the results of the STARTER trial found a graded clinical response that varied as a function of the distance between the echocardiographically-demonstrated point of latest ventricular mechanical activation and the final location of the CS lead.[37] An alternative approach that may work better within the confines of the CS relies on finding the area of latest electrical activation.

Strategies For Pacing At Sites Of Latest Electrical Activation

The two main modalities available for determining the site of latest electrical activation include intraoperative measurements of the electrical delay with the catheter positioned in the various CS tributaries and inverse electrocardiographic imaging using body-surface mapping electrodes.

The most commonly employed method of finding the area of most delayed ventricular electrical activation involves intraoperative measurements of the QLV interval in each of the CS tributaries. The QLV interval is defined as the time elapsed between the beginning of the QRS complex on surface ECG and the onset of the sensed electrogram at the LV lead as a fraction of the total QRS interval. This approach has been validated and studies have shown that placement of the CS lead at the site of longest QLV interval was correlated with improved hemodynamics, including higher maximum dP/dT.[38] In addition, a substudy of the SMART-AV trial showed that the length of the QLV interval is predictive of response to CRT, in that patients with greater electrical dyssynchrony reflected by a longer QLV interval experience more improvement with CRT.[39] Similar results were observed in the MADIT trial.[21] This method has the benefits of requiring minimal additional intraoperative time and no ancillary studies such as speckle-tracking echo or cardiac MRI. The fact that the QLV interval can only be measured in the tributaries

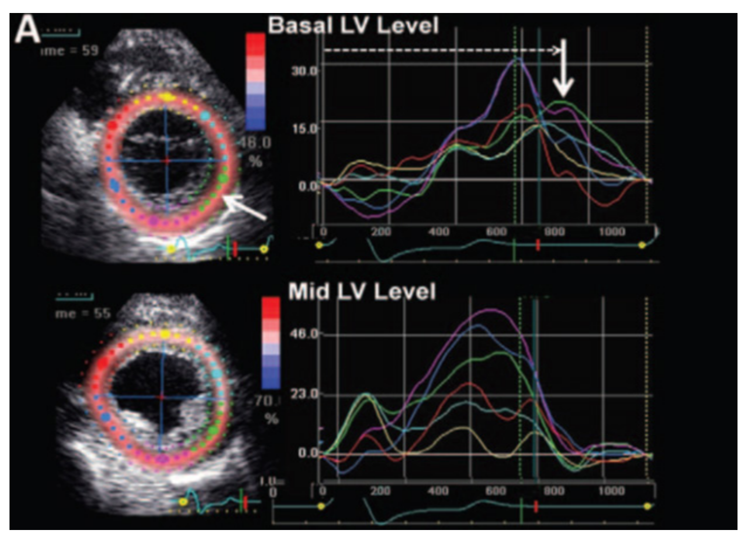

Figure:2 An example of speckle tracking to assess sites of latest mechanical activation (white arrow), from the STARTER trial (Reference 28).

of the CS which are catheter-accessible is not a disadvantage of the method because it is only those catheter-accessible regions that are available for placement of the CS lead. Currently, several additional studies are underway correlating QLV interval as measured at the CS lead and clinical and echocardiographic response to CRT.

Inverse electrocardiographic imaging (iECG) serves to non-invasively estimate the electrical potentials along the epicardial surface to determine the patterns of conduction delay, thereby inferring optimal locations for lead placement based on areas of latest electrical activation. Compared to the other modalities discussed above, iECG is earlier in development and in application to patients in clinical studies.

Combined And Alternative Approaches

Since these modalities for pre-implantation assessment have complementary strengths, a multimodality approach is currently being trialed, comparing QLV-guided LV lead placement with image-guided placement using speckle-tracking echo, SPECT, and cardiac CT.[40] Although the imaging will facilitate pacing at sites of latest electromechanical activation and this is preferred to deciding based on population-level data, even better outcomes may be achieved when the entire endocardial surface is surveyed for optimal response via intraventricular roving catheter. In our institutional experience, 8 of 11 patients who underwent intraoperative hemodynamic measurements while being paced at various endocardial surfaces were found to have an optimal pacing site that was not at traditionally used locations for LV pacing.[20] While previous investigations have partially attributed this differential response to endocardial versus epicardial pre-excitation,[41, 42] we found that the improved hemodynamic response was due to more choices in locating the optimal site, rather than endocardial pacing per se; pacing at endocardial sites adjacent to epicardial sites yielded similar hemodynamic results. While promising, the relationship between optimal intraoperative hemodynamic response and long-term clinical outcomes needs further exploration. Notably, determination of optimal pacing site is of limited utility as long as operators are constrained by the distribution of the CS.

Conclusions

In most patients, CRT leads to improved hemodynamics, echocardiograpic parameters, and clinical outcomes. Despite this, a subset of patients are non-responders. Even among those who do derive a benefit, we seek to maximize response. To these ends, there may be a role for patient-tailored therapy via image-guided LV lead placement. While LBBB on surface ECG remains critical for identifying patients most likely to benefit, studies to date have demonstrated the incremental value of echo and cardiac MRI in targeting the latest-activated myocardium and avoiding regions of scar. As developing technologies such as multipolar leads, endocardial leads (among the permanently anticoagulated), and fully intracardiac leadless pacemakers become more readily available, our therapeutic armamentarium grows and we will be able to individualize each patient's treatment based on their cardiac anatomy to optimize outcomes.[43, 44] The science of patient-specific lead placement remains in its infancy and much work remains to be done, but perhaps one day the concept of "non-responders to CRT" will be obsolescent.

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