Identifying CRT responders: Moving from electrical to mechanical dyssynchrony

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Cardiac resynchronization therapy (CRT) has been a cornerstone in the treatment of advanced, medically refractory heart failure.[1] Studies evaluating CRT have shown reduction in mortality, reduction in HF hospitalizations, and improvement in functional outcomes, and therefore, carry a class I indication per the 2013 ACCF/AHA guideline on management of heart failure, among those with left bundle branch block (LBBB).[2] Delayed left ventricular (LV) free wall activation has long been thought to be the hallmark of LBBB. Resynchronization therapy, therefore, is directed to recruiting the LV free wall, which is the premise of LV lead placement in a lateral branch vein of the coronary sinus. Despite showing promising improvements in LV function and reverse remodeling in selected patients, up to 30-35% of patients do not derive a positive CRT response.[3] This could be due to a combination of several factors—infarct size, non-LBBB activation pattern, and lack of adequate coronary sinus venous anatomy.

While the landmark CRT trials used QRS duration and not QRS morphology as their inclusion criterion, the QRS morphology had been used as a means to define subgroups and has subsequently been adopted in European and North American guidelines.[4–6] Although long-term follow-up from MADIT-CRT did show that patients without evidence of LBBB have reduction in subsequent heart failure hospitalizations,[7] majority of studies showed no benefit and even poorer outcomes in patients with CRT who did not have LBBB.[8,9] Therefore, evidence of electrical dyssynchrony with LBBB on EKG has been the default approach to patient selection. While LBBB has several definitions, Stipdonk et al. found no difference in discriminatory capacity between responders and non-responders using different LBBB definitions,[10] and other studies[11,12] have reported that using stricter definitions for LBBB including QRS notching in 2 or more contiguous leads fare better in identifying CRT responders.

Are markers of electrical dyssynchrony enough to identify CRT responders? In this issue, He et al.[13] report data from a retrospective analysis of patients evaluated between May 2009 and August 2020 with either dilated (DCM) or ischemic (ICM) cardiomyopathy who met indications for CRT placement. All patients underwent baseline transthoracic echocardiogram and gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). The onset of mechanical contraction and relaxation throughout the cardiac cycle were obtained by multi-harmonic Fourier approximations and left ventricular mechanical dyssynchrony (LVMD) was represented by phase distribution of systolic activation and diastolic relaxation of the left ventricle, and quantitative parameters LVMD were calculated—phase standard deviation and phase bandwidth. Right atrial and ventricular leads were placed via conventional approaches, and the LV lead location was determined by coronary venous angiography and then correlated to the 13-segment polar map of the systolic and diastolic dyssynchrony. A total of 142 patients (DCM, 92; ICM, 50) who underwent SPECT MPI before CRT implantation were included in this study, and baseline characteristics were comparable in the two groups. Patients had a mean follow-up time of 39 ± 24 months. Patients were divided into 3 groups, those with LV lead adjacent to both latest contraction and relaxation (both match), those where LV lead was adjacent to

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either latest contraction or relaxation (one match) or those where there LV lead was not adjacent to either (no match). A response to CRT was defined as an increase in LVEF by 5% or more. This definition of CRT response used in the current study seems less clinically relevant in comparison to LV end systolic volume (LVESV) change of >15% which was used in major clinical trials. The authors reported a significant difference in CRT response between these 3 groups in the DCM group but not in the ICM group. Although the event rates were small in number, Kaplan-Meier survival curves showed significantly longer survival in DCM patients with the concordance between LV lead location with the latest contraction and relaxation position (P = 0.050). However, there is no significant difference of survival time in ICM patients based on the concordance between LV lead and the latest contraction or relaxation position. Interestingly, despite knowledge of the sites of latest activation and relaxation from SPECT MPI, LV lead was adjacent or concordant to this site in only 22% of the patients (18 in DCM group and 24 in ICM group). This has remained the Achilles heel of imaging parameters to identify mechanical dyssynchrony that despite the ability to identify the ideal site of LV free wall pacing, the lead placement may be unpredictable in light of variable coronary sinus venous anatomy.

This differential response to CRT has been a cause of substantial debate. While the effects of CRT on morbidity and mortality are seen irrespective of etiology of heart failure,[14] the magnitude of reverse remodeling with CRT occurs more favorably in DCM when compared to ICM.[15–18] ICM patients tend to be older with more advanced heart failure, worse kidney function, and overall have shorter life expectancy when compared to DCM.[19] This was studied in a large retrospective CRT cohort by Kloosterman and colleagues[20] who found that ICM patients, despite achieving lesser reverse ventricular remodeling, have a similar prognostic gain, in terms of survival time, compared with DCM patients for every single percentage of achieved reverse remodeling. Other factors such as improvement in diastolic function[21] that is seen with DCM and effects of burden of ischemic scar on CRT response, and worse outcomes in ICM have been reported previously,[22–24] and are in line with the results of this present study. An additional factor, which is more likely related to effective pacing, is the presence of greater scar burden among those with ICM. Adelstein and colleagues have previously shown that a scar burden of >40% was associated with poor CRT response in ischemic cardiomyopathy.[25]

It is safe to assume that the benefit of CRT can only be seen if several essential prerequisites are met. First, there is evidence of mechanical dyssynchrony, with septal-to-lateral wall delay and the posterolateral LV wall being the site of latest activation or relaxation during intrinsic conduction, as seen among those with LBBB. In those without LBBB, the site of latest activation (SOLA) could be located in a region other than the lateral wall. Second, it is essential to quantify the scar burden, and if < 40%, then to identify the site of latest activation (SOLA) in areas of viable myocardium. The burden of scar, the presence of dyssynchrony, and SOLA can be readily evaluated by routine gated SPECT MPI. Once these conditions are met, then the task would be to place the LV lead at or adjacent to the SOLA. Information from gated SPECT MPI can be combined with intraprocedural coronary sinus venogram to guide adequate LV lead placement.[26] Coronary sinus venous anatomy can also be assessed by computed tomography, prior to performance of the procedure.[27] If LV lead cannot be optimally implanted despite a myocardial substrate being favorable for resynchronization, then CRT will likely be ineffective. An algorithm for selection of patients for optimal benefit from CRT is provided in the Figure 1.

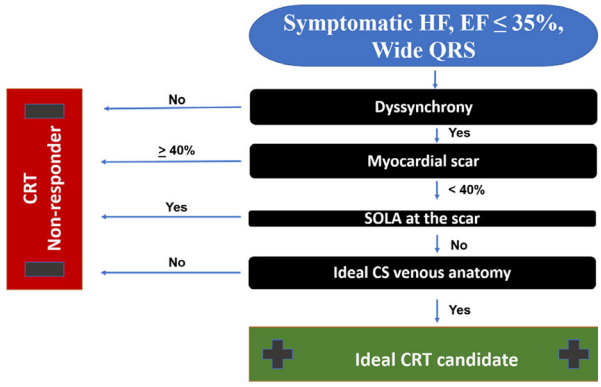

Figure 1. A scheme for patient selection for optimal benefit after cardiac resynchronization therapy.

Disclosures

Dr. Vij—none; Dr. Malhotra—Speaker's bureau: Pfizer and Alnylam; Advisory board: Alnylam and Bridgebio.

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