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EDITORIAL COMMENT

Is the Magnet a Better Crystal Ball for Predicting Response to Cardiac Resynchronization Therapy?*

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Cardiac resynchronization therapy (CRT) is undoubtedly of great benefit to many heart failure patients with widened QRS and depressed ejection fraction (1–3). The pathological feature that appears to be a large reason for response to CRT is correction of abnormalities of timing in regional left ventricular (LV) mechanical activation, known as dyssynchrony (4). Improvements in synchrony of regional LV contraction results in hemodynamic improvements, decreases in mitral regurgitation, and LV reverse remodeling (4–6). However, a consistent proportion of patients who undergo CRT do not seem to respond favorably, either with an improvement in clinical symptoms or LV function. The prevailing hypothesis has been that patients who are nonresponders to CRT are in large part those curious individuals who have QRS widening, but no significant dyssynchrony (7). The

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relationship of dyssynchrony and response to CRT appears logical because septal and free-wall biventricular pacing cannot improve mechanical dyssynchrony if it is not present in the first place. Furthermore, there is preliminary evidence that patients may be potentially harmed by CRT, if they lack mechanical dyssynchrony before pacemaker implantation. Although the dyssynchrony argument is compelling, we have learned that the absolute classification of dyssynchrony versus no dyssynchrony is too simplistic because alternate reasons exist for nonresponse, such as suboptimal lead placement, scar burden, disease progression, or disease resolution unrelated to CRT (8–10).

The interesting study by Bilchick et al. (11), which appears in this issue of *iJACC (JACC: Cardiovascular Imaging)*, utilized cardiac magnetic resonance imaging (CMR) myocardial tissue tagging (MT) to quantify mechanical dyssynchrony in CRT patients. At the same time, gadolinium contrast-delayed enhancement-cardiac magnetic resonance (DE-CMR) qualified scar burden and was combined with dyssynchrony information as a means to separate responders from nonresponders to CRT. Although this approach was only tested in a pilot group of 20 CRT patients, the combined assessment of scar burden and circumferential dyssynchrony was remarkably predictive of CRT response in this initial sample. This human study extended the group's previous CMR-MT work from a canine model similarly demonstrating that short-axis dynamics assessed as circumferential strain were superior to longitudinal dynamics for quantifying dyssynchrony associated with left bundle branch block (12). The present study also found circumferential strain by CMR-MT to be superior to measures of tissue Doppler longitudinal velocity. The utility of short-axis dynamics to longitudinal dynamics for dyssynchrony assessment has also been supported by previous human studies using speckle tracking radial strain echocardiographic imaging (13,14). Although the precise reason for this observation is not known, it appears that the abnormalities in septal free-wall mechanical activation are easier to detect in the short-axis plane, as compared with detection of dyssynchrony in the longitudinal plane (15).

This CMR study supports the hypothesis that lack of dyssynchrony is an important reason for nonresponse and adds the quantification of extent

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of scar by DE-CMR to refine identification of nonresponders. Although these results are logical and supported by previous work, this specific study is preliminary with a sample of only 2 patients with significant dyssynchrony by CMR-MT who were nonresponders, and only a single patient with dyssynchrony had significant scar burden by DE-CMR. Accordingly, the actual additive value of DE-CMR to CMR-MT remains to be tested clinically.

What is the ideal cardiac imaging method and analytical approach to identify responders to CRT? The accurate identification of responders from nonresponders would be of great clinical benefit because CRT is expensive and not without risk of a serious complication. Current clinical criteria do not support the use of an imaging technique before CRT for patient selection, other than assessing ejection fraction (16). However, a great deal of interest and effort has been devoted to investigating cardiac imaging methods to detect and quantify cardiac dyssynchrony in an attempt to improve patient selection for CRT over the current selection guidelines using electrocardiographic QRS width. Alternate cardiac imaging methods including radionuclide, CMR, and a wide variety of echocardiographic methods have been reported to predict CRT response to variable degrees (7,13,17–21). Echocardiography appears well suited for the assessment of dyssynchrony because of favorable temporal and spatial resolution and wide availability. The greatest volume of published reports has been using echo-Doppler methodology. However, a recent multicenter study, known as the PROSPECT (Predictors of Response to CRT) trial, failed at its goal to determine which echocardiographic method was superior in predicting response to CRT (22). It revealed technical problems that can exist with M-mode, tissue Doppler, and other echocardiographic methods with respect to yield in consecutive patients and variability among observers. This has generated current controversy as to the utility of echocardiographic methods to predict response to CRT. Unfortunately, there were many problems with the PROSPECT study, including patient selection and confounding variables of multiple vendors, multiple software approaches, and multiple core laboratories, which resulted in a nonuniformity of data collection and analysis. Despite the uncertainly of how these issues affected the PROSPECT study results, an important lesson learned was that dyssynchrony imaging analysis is a complex task that is technically demanding and requires a high level of expertise. Although a simple highly sensitive and specific echocardiographic method for predicting response to CRT has not been established, practical guidelines exist (7), and hope for future refinements remains.

Can CMR be a clinical tool to assist in patient selection for CRT? The ability of CMR to assess scar burden in addition to quantifying dyssynchrony is a clear advantage to routine echocardiographic methods, since wall thickness and visual assessment of wall thickening are poor means to quantify scar. However, there are many challenges that CMR still must face to become part of mainstream clinical practice for the pre-CRT assessment. The CMR-MT data presented in the study by Bilchick et al. (11) are the result of this group's extensive experience in applying this technically sophisticated methodology. Although the data acquisition for CMR-MT appears to be straightforward, the analysis of tagged strain requires specialized software, and a sufficient level of expertise and knowledge of cardiac mechanics to yield meaningful results. In this sense, CMR-MT may be potentially more difficult than echocardiographic methods for the clinician. Fears with CMR scanning of patients who have undergone pacemaker implantation remain, and this also limits follow-up study for comparison. Finally, availability of CMR-MT remains a limitation for many clinical settings, whereas echocardiography is most widely available.

In summary, the volume of evidence that cardiac imaging may assist in patient selection for CRT by providing quantitative dyssynchrony and scar burden information is compelling. The precise imaging approach has not yet been elucidated, and the routine selection criteria using electrocardiography remain. Although the body of data using echocardiographic techniques far exceeds that for CMR-MT, issues regarding feasibility and variability still need to be resolved. An intense focus on technological improvements in echocardiographic dyssynchrony methods remains in order to produce robust and reproducible results in a simplified manner for the future. CMR imaging has great potential to assist in patient selection for CRT, but like echocardiography, these specific methods need to be prospectively tested in a multicenter setting before they may become the routine crystal ball to predict response to CRT in mainstream clinical practice.

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