News and Views From the Literature

Cardiac Resynchronization Therapy

A Perspective on PROSPECT and the Continued Search for Predictors to CRT Response

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Results of the Predictors of Response to CRT (PROSPECT) Trial

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Cardiac resynchronization therapy (CRT) is a device therapy that has gained worldwide acceptance as adjuvant treatment of patients with severe refractory heart failure (HF).[1,2] Patients with New York Heart Association (NYHA) functional class III or IV HF, severe left ventricular (LV) systolic dysfunction (ejection fraction ≤ 35%), and prolonged QRS duration (≥ 120 ms) who are treated with CRT have shown significant improvement as compared with patients treated with medical therapy alone, with as much as a 40% reduction in major adverse coronary events and all-cause mortality in the Cardiac Resynchronization in Heart Failure (CARE-HF)[3,4] and Comparison of Medical Therapy, Pacing and Defibrillation (COMPANION)[5] trials. CRT involves implantation of a biventricular device (either a pacemaker or a defibrillator) that can simultaneously pace the right atrium, right ventricle, and left ventricle, and thus "resynchronize" the heart. By resynchronizing the ventricular contraction, global LV function improves.

However, about 30% of CRT patients demonstrated no clinical improvement or continued to deteriorate.[6-8] A leading contributor to CRT nonresponse is believed to be intraventricular dyssynchrony.[7,8] Intraventricular (or LV) dyssynchrony occurs when there is delayed electromechanical activation within regions of the left ventricle that results in discordant and inefficient contraction. It is postulated that CRT responders have a greater degree of LV dyssynchrony as compared with nonresponders and that LV dyssynchrony may be an independent predictor of CRT response. Although a prolonged QRS duration of 120 ms or more has been used as a surrogate marker for interventricular dyssynchrony (delayed activation between the right and left ventricle), it is an unreliable indicator for LV dyssynchrony and a suboptimal predictor for response to CRT.[7,8] Several noninvasive imaging modalities have tried to establish a reliable measure of dyssynchrony that is predictive of CRT response. Two-dimensional (2D) echocardiography is the most studied of the imaging modalities. However, controversy exists based on the small single-center studies and the numerous echocardiographic measurements with various techniques (traditional M-mode and pulsed Doppler, tissue Doppler imaging, and strain).

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The PROSPECT Trial

The Predictors of Response to CRT (PROSPECT) trial was a prospective, multicenter, observational study that aimed to evaluate 12 commonly used baseline echocardiographic dyssynchrony parameters and correlate them to patients' clinical and echocardiographic responses to CRT.[9] This study was conducted in 53 international centers with 3 core echocardiography laboratories from March 2004 to December 2005 and included 426 chronic HF patients on medical therapy. Inclusion criteria included an LV ejection fraction at or less than 35%, NYHA functional class III or IV heart failure, and QRS duration of 130 ms or more. A positive response at 6 months was defined as an "improved" HF clinical composite score (CCS) or a reduction of LV end-systolic volume (ESV) by at least 15%. Among the study subjects, 71% were men (average age, 68 years), 96% had NYHA class III HF, and 54% had ischemic cardiomyopathy.

Of the 426 patients, CCS in the 6-month follow-up period improved in 69%, was unchanged in 15%, and worsened in 16%. Of the 286 patients with both baseline and 6-month repeat LV ESV measurements, 56% improved (with a reduction in LV ESV of at least 15%), 9% worsened (with an increase in LV ESV of 15% or more), and 35% had no change.

The authors used receiver-operating characteristics curve analysis with area under the curve (AUC) to determine the discriminatory power of these echocardiographic parameters. An AUC value can range from .50 to 1.0, with .50 considered nondiscriminatory and similar to a coin toss and 1.0 considered a perfect predictive value and discrimination. Unfortunately, of the 12 dyssynchrony parameters, the AUC for predicting clinical response with either CCS or LV ESV ranged from .50 to .62. These values are suboptimal. Moreover, despite the fact that clinicians at all of the centers were trained in the standardized echocardiographic protocols, there were major issues of poor intraobserver reproducibility (coefficient of variation, 11%-24%), interobserver reproducibility (coefficient of variation, 32%-72%; κ, .15 to .35), and inevaluable echocardiograms (with interpretability ranging from 37%-95%). Thus, the authors concluded that none of the 12 established 2D echocardiographic dyssynchrony parameters had sufficient value for predicting CRT response.

Therefore, the search for potential responders to CRT with echocardiography and other noninvasive imaging modalities continues. There appears to be no "perfect" imaging modality because all have 1 trade-off or another. More advanced echocardiography techniques, such as 2D speckle tracking strain imaging and 3D echocardiography, have been used, and initial reports from experienced single-center sites show a correlation to the CRT response.[10-12] However, these newer echocardiography measures may have many of the same challenges intrinsic to those 2D echocardiography parameters studied in PROSPECT with regard to operator dependency, adequate acquisition windows, varying angle planes, and poor spatial resolution. Nuclear imaging studies, which use phase image analysis, have the constraints of poor spatial resolution and radiation exposure.[13,14] Both cardiac magnetic resonance (CMR) imaging and computed tomography (CT) provide excellent spatial resolution, and electrocardiogram-gated protocols allow for 3-dimensional assessment of LV contractile function. Although CMR has great potential for dyssynchrony assessment, its general applicability may be limited by long scan time (typically > 45 min), which may be difficult for NYHA class III and IV patients to tolerate, complex protocols that require highly trained cardiac imagers, metal incompatibility, and few available centers (CMR scanners are available mainly at large tertiary referral centers).[15,16] Cardiac CT may have issues related to radiation and limited temporal resolution (with the 64-slice CT scanners), but it has the potential to be used for dyssynchrony assessment with the faster CT scanners (eg, dual-source CT) and with multisegment reconstruction algorithms, and it could provide an expeditious alternative to CMR.[17,18] The issue of radiation with nuclear imaging and cardiac CT may be less of a concern in this high-risk HF population, in which the 5-year mortality is 50%, and 1-year mortality can be as high as 44% for patients with NYHA class IV HF.[19,20] Currently, all imaging modalities for dyssynchrony are considered investigational. There remains no gold standard, and there is still an essential need for a reliable measure for this assessment.

Questions to Consider

Data regarding CRT bring up several questions to consider. Is CRT response due solely to dyssynchrony, or are there other factors that may contribute to this clinical dilemma? Some researchers have postulated that the response rate may be directly influenced by LV lead placement and the site of pacing. Should regions of scar tissue be avoided, as suggested by CMR and nuclear studies, or is the more important factor the total scar burden—or is it a combination of both?[21-28] Should the optimal pacing site be targeted at the region with the most dyssynchrony or delayed activation?[12,29] Might triple-site pacing with 2 LV leads and 1 right ventricular lead be superior to dual-site pacing with the conventional single LV lead and right ventricular lead?[30] How important is preknowledge of the coronary venous anatomy?[31,32] Is it sufficient to know the large coronary venous tributaries (which can be visualized by both CMR and CT) or would secondary and tertiary tributaries be necessary, which may only be visualized with higher spatial resolution CT?[33-35] Although the answers to these questions may for now be uncertain, the use of imaging and CRT holds much promise in this patient population. ■

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