

EDITORIAL COMMENT

Examining Achilles' Heel

Improving Response Rates With Cardiac Resynchronization Therapy*



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Clinical trials evaluating cardiac resynchronization therapy (CRT) have demonstrated improved heart failure status, quality of life, exercise capacity, systolic function of the left ventricle (LV), mortality, and numerous other outcomes in heart failure patients (1,2). Current guidelines recommend CRT for heart failure patients with LV ejection fraction (EF) <35%, New York Heart Association functional class I to III symptoms on optimal medical therapy, and QRS duration ≥ 120 ms on the surface electrocardiogram. Although most patients respond to CRT, up to 30% of patients meeting implant criteria fail to show clinical benefit. This rate of CRT nonresponders has been represented as the “Achilles’ heel” of CRT. Multiple investigations have focused on techniques of optimizing LV lead position to improve response rates. Although the evidence supporting CRT is robust, the inability to develop proven techniques to optimize LV lead position and improve outcomes remains a notable weakness.

Because QRS duration and morphology have been inclusion criteria for CRT clinical trials, these and other purely electrical parameters of global and regional depolarization have been evaluated as predictors of CRT response (3,4). Patients with left bundle branch block (LBBB) and more prolonged QRS durations have better response rates with improved hemodynamics, clinical outcomes, and LV reverse remodeling (3). LV electrical delay is considered to be an important factor in predicting response to CRT (3). Recent investigations of electrical dyssynchrony, as evaluated by the time interval between the initial deflection of the surface electrocardiogram QRS and

local LV activation at the LV stimulation site (QLV), indicate a strong and independent association with reverse remodeling and other outcomes with CRT (4).

In addition to these electrical parameters, the anatomic position of the LV lead has been demonstrated to have a profound influence on clinical response (5). The lateral or posterolateral branches of the coronary sinus have most consistently resulted in restoration of coordinated myocardial contraction (5). However, even with appropriate anatomic lead placement, there remains considerable individual variation in response. A substantial proportion of patients fail to respond, despite optimization of electrical and anatomic parameters (5). Both the location and amount of mechanical dyssynchrony, reflecting distribution and extent of myocardial scar relative to the LV lead position, have been found to be important in selecting optimal LV lead position. Retrospective cardiac magnetic resonance imaging and single-photon emission computed tomography (SPECT) studies have demonstrated an unfavorable outcome after CRT when the LV lead is positioned in areas with transmural myocardial scar (6,7).

Multiple studies indicate that LV pacing placement might be refined with assessment of LV regional mechanical dyssynchrony (6,7). The effects of resynchronization can be optimized when the LV is paced at the site that is most delayed on the basis of mechanical rather than anatomic location or electrical activation (6,7). Preliminary investigations indicated that pacing the most mechanically-delayed LV region improves response rates to CRT. Assessment of mechanical dyssynchrony, identified as the latest activated LV myocardial segment, has been performed by multiple imaging techniques. These include echocardiography and Doppler techniques, SPECT, cardiac magnetic resonance imaging, and cardiac computed tomography. Promising results on CRT outcome were reported in an initial prospective study evaluating the effect of speckle-tracking echocardiography to optimize LV lead

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placement, but have not been reproduced in larger studies (6,7).

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In this issue of *iJACC*, Zhou et al. (8) report on a novel approach to selecting the site of LV pacing by assessing viable regions of myocardium with late activation (8). Using a novel technique of 3-dimensional fusion of LV venous anatomy with fluoroscopic venograms on SPECT myocardial perfusion images, the investigators used landmark-based registration and vessel surface overlay to fuse the venous anatomy with the epicardial surface (8). The accuracy of the technique was validated with computed tomography venograms (8). Thus, the feasibility of this approach to guide LV lead placement was reported in a small series of patients. Although the investigators conclude that this technique is technically accurate and feasible, it is evident that additional research is needed (8). The data presented are adequate for validating technical accuracy and demonstrating feasibility, but the effect of this technique on response rates to CRT and clinical outcomes remains to be determined. This study needs to be confirmed with additional patients and meaningful assessment of clinical outcomes. Prospective multicenter trials ultimately would be necessary to fully assess the clinical utility of the technique (8). This novel technique of optimizing LV lead placement detailed in this issue, like other electrical, anatomic, or mechanical techniques, has not met the standards of evidence-based medicine by demonstrating improved response rates in appropriately-designed clinical trials.

Although the focus on optimizing techniques of LV lead placement to improve CRT response rates is appropriate, clinicians and investigators should also examine the issue of CRT nonresponders from a broader perspective. Heart failure patients with

an LBBB derive substantial clinical benefit from CRT-defibrillator, with a reduction in heart failure progression and a reduction in the risk of ventricular tachyarrhythmias. By contrast, no clinical benefit has been observed in patients with a non-LBBB QRS pattern (right bundle-branch block or intraventricular conduction disturbances). Subgroups of patients with QRS widths ≥ 150 ms consistently demonstrate the greatest decrease in heart failure events, reduction in LV volumes, and improvement in LVEF. Females have considerably higher response rates to CRT than males. Patients with nonischemic cardiomyopathy respond more frequently than those with ischemic heart disease. Patients in sinus rhythm demonstrate response rates considerably higher than those in atrial fibrillation. Multiple analyses have concluded that there is a threshold effect with respect to percent LV pacing. Patients with 95% LV pacing or more have response rates that are higher than those pacing <95%. Assessment of ineffective resynchronization from fusion or pseudo-fusion beats during LV pacing with ambulatory monitoring can provide useful information that allows for improved CRT response rates. Novel techniques of AV optimization, multisite endovascular LV epicardial pacing, and LV endocardial pacing including leadless LV pacing may provide innovative approaches to improving CRT response rates (9). As investigations of these and other novel approaches to the "Achilles' heel" of CRT move forward, clinicians and investigators should be mindful of the existing robust evidence related to patient selection and pacing techniques currently known to improve response rates.

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