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EDITORIAL COMMENT

Will the Real Left Bundle Branch Block Please Stand Up?*

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In 1925, Dr. Carl J. Wiggers demonstrated that pacing from the canine left ventricle (LV) improved acute hemodynamics (1). The advent of pacing catheters delivered by the coronary sinus allowed practical use and exploration of LV or biventricular (BiV) pacing for improving heart failure (HF) symptoms. By 2000, BiV pacing was performed in 17 patients with New York Heart Association (NYHA) functional class III to IV HF and electrical dyssynchrony (electrocardiography [ECG] QRS duration >140 ms) followed for 3 months. The results demonstrated improvements in serial echocardiographic measures of ejection fraction (EF), mitral insufficiency, dP/dt, and LV volumes, which regressed following termination of BiV pacing (2).

Since this trial, over 4,000 NHYA functional class III to IV and over 4,500 NYHA functional class I to II patients have been evaluated in randomized controlled trials of cardiac resynchronization therapy (CRT), with 4 consistent themes: 1) most patients improve clinically, and roughly 25% are "nonresponders" (the same failure rate observed for contemporary pharmacological HF therapy); 2) most trials used a wide QRS duration (QRSd), although with variable cutoffs (≥120, ≥130, or ≥150 ms) as the measure of *electrical* dyssynchrony; 3) echocardiographic measures of *mechanical* dyssynchrony were rarely used as an enrollment strategy; and 4) patients with narrow QRSd (≤120 or ≤130 ms, especially with non-left bundle branch block [LBBB]), show poor response to CRT in limited studies. Mortality was not the primary endpoint in any of the trials; all combined endpoints emphasized symptomatic and functional improvements. Decreased mortality as a secondary endpoint was notably seen in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) and CARE-HF (Cardiac Resynchronization–Heart Failure) trials (3,4).

Thus, QRSd was the foundational enrollment criterion for the CRT trial. Although few patients with a right bundle branch block were enrolled, the observation that patients with either a right bundle branch block or a nonspecific intraventricular conduction delay demonstrate inferior outcomes compared with those with LBBB has been made more recently from the 3 trials (REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction] [5], MADIT-CRT [Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy] [6], and RAFT [Resynchronization-Defibrillation for Ambulatory Heart Failure Trial [7]) that enrolled NYHA functional class I to II patients. All 3 showed benefit of CRT-implantable cardioverter-defibrillator therapy compared with implantable cardioverter-defibrillator alone on the basis of outcomes of decreased HF events and composite endpoints and found that QRSd (≥160 ms in RAFT [8,9] and ≥150 in the MADIT-CRT) and QRS *morphology*, specifically LBBB, were predictive of a superior outcome. This morphology finding from MADIT-CRT led the U.S. Food and Drug Administration to restrict device labeling for NYHA functional class I and II HF patients with LBBB and influenced reconfiguration of the U.S. and European guidelines to emphasize QRS morphology beyond QRSd.

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Finally, 3 major trials have addressed narrow QRSd dyssynchrony (10–12). The largest, EchoCRT (Echocardiography Guided Cardiac Resynchronization Therapy) (12), concluded that narrow QRS dyssynchrony, despite evidence of mechanical dyssynchrony by echocardiography, does not respond favorably to CRT. In EchoCRT (NYHA functional class III to IV, EF ≤35%, LV end-diastolic diameter ≥55 mm, QRSd ≤130 ms, and echocardiographic evidence of dyssynchrony), there was a nonsignificant trend toward worsening in patients randomized to CRT on the primary composite endpoint (death or first hospitalization) and clearly more deaths (a secondary endpoint: 11.1% vs. 6.4%; p = 0.02).

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In this issue of the *Journal*, Risum et al. (13) attempt to transcend even QRS morphology to refine selection of "optimal" CRT candidates. In their study, 234 patients with QRSd ≥120, LVEF ≤35%, NYHA functional class II to IV, and an LBBB pattern on ECG underwent an evaluation of LV dyssynchrony by longitudinal strain imaging utilizing 2-dimensional speckle tracking echocardiography (2DSE). Instead of using the time-to-peak principle, as in previous studies to predict response to CRT, most notably PROSPECT (Results of the Predictors of Response to CRT) (14) and EchoCRT (12), the authors used a prespecified longitudinal strain pattern recognition of LBBB. Subjects were considered to have a true LBBB if all 3 of the following echocardiographic characteristics were present: 1) "early" shortening of at least 1 basal or midventricular segment in the septal wall; 2) early septal peak shortening (within the first 70% of ejection phase); and 3) lateral wall peak shortening after aortic valve closure. The authors conclude that this method is superior to previously used methods in that the interobserver and intraobserver variability was excellent, with kappa agreement scores of 1.0 and 0.87. In contrast, intraobserver and interobserver agreement in the PROSPECT trial, as measured by the coefficient of variation, was poor (as high as 16% and 72%, respectively). Risum et al. (13) found that, despite an LBBB on ECG defined by *conventional ECG criteria*, more than one-third of patients did not show the 2DSE pattern of "true" LBBB contraction. During a 4-year follow-up, patients with the LBBB contraction pattern by 2DSE had fewer composite events (death, transplant, or need for LV assist device placement) than those without an echocardiographically-defined LBBB contraction pattern (14% vs. 40%; hazard ratio: 3.57; 95% confidence interval: 2.00 to 6.66; p < 0.001). The c-statistic for estimating risk increased from 0.63 to 0.70 when adding the LBBB pattern by 2DSE (p = 0.02).

Also notable was that only 30% of patients with a QRSd between 120 and 140 ms had LBBB contraction using 2DSE, compared with 65% of patients with QRSd >140 ms. The LBBB pattern of contraction by 2DSE was also superior even to the "strict" ECG LBBB pattern recently described by Strauss et al. (15). Finally, when taking multivariable models into account, comparing the LBBB pattern of contraction by 2DSE was superior to older time-to-peak methods using tissue Doppler imaging, longitudinal and radial strain, and tissue Doppler imaging opposing wall dyssynchrony.

The study by Risum et al. (13) emphasizes the limitations of conventional ECG-defined LBBB in detection of true mechanical dyssynchrony and provides initial evidence that a combination of electrical dyssynchrony by ECG and echocardiography-defined LBBB to detect mechanical dyssynchrony could enhance the selection process for CRT.

However, HF patients are complex, and it is not surprising that many with apparent LBBB will not have mechanical dyssynchrony as defined by the echocardiographic measures used in this study. The variable presence of scar versus viable myocardium, including in the lateral wall, affects contraction patterns. The lateral wall may not be the latest myocardial segment activated, such that resynchronization may be achieved by alternatively locating the LV lead. Gold et al. (16) have used the QLV measurement to allow consideration of such variables for identification of the optimum LV pacing site at the time of CRT implant.

Thus, on the basis of the authors' findings, one might conclude that defining "true" LBBB by echocardiography is the final answer for CRT selection. Should we believe this? Such patients may be "super-responders," as observed in a MADIT-CRT substudy, but many more patients may benefit from CRT. Approximately 80% of MADIT-CRT LBBB patients were responders or super-responders, defined by LVEF improvements or the primary combined outcome of nonfatal HF events or all-cause mortality (17).

A more significant caveat is whether the findings of Risum et al. (13) are generalizable to the global practice of echocardiography. Use of strain is expanding, and it is close to disseminated use. For the immediate future, strain will be mainly used in academic laboratories for research purposes. Even frequent users may have some difficulty reproducing the authors' LBBB findings. Late lateral wall contraction (after aortic valve closure) in particular can be a nonspecific finding, seen in 31% of segments from 20 normal young patients (18). Additionally, the early septal peak shortening of 70% is unlikely to be precisely quantified. Finally, strain measurements have significantly varied between different vendors of echocardiography machines. The good news is: 1) the current study used only 1 type of echocardiography machine; 2) the variation has been significantly reduced (19); and 3) definition of LBBB by 2DSE is based more on timing than percent strain, much less subject to intervendor variation.

Thus, putting the clinical implications of the study by Risum et al. (13) into final context gives us pause. We applaud the authors for making a significant advancement for the credibility of echocardiography in determination of mechanical dyssynchrony. But, did the real LBBB stand up, or is the “truth” still untold (20) (except to Alex Trebek).

As the authors also suggest, we believe that confirmation by a randomized trial that included not only the hard endpoints of mortality and HF events, but also the standard measures of quality of life, LV volumes, and functional measurements such as 6-min walk or VO_2 would best serve adoption of this approach by clinicians and the guidelines committees.

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