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EDITORIAL COMMENT

QRS Width and Mechanical Dyssynchrony for Selection of Patients for Cardiac Resynchronization Therapy

One Can't Do Without the Other*

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Cardiac resynchronization therapy (CRT) in patients with therapy-resistant, symptomatic heart failure in the setting of reduced left ventricular (LV) ejection fraction and wide QRS complex provides symptom relief, induces reverse remodeling, and improves survival (1–3). Because approximately 30% of patients fulfilling standard selection criteria for CRT do not experience such benefits, there has been substantial interest in identifying a method or parameter that predicts which patient would respond best to CRT.

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The biological value of CRT is believed to be the synchronization of dyssynchronous mechanical contraction of the LV, associated with progressive dilation and electrical remodeling of heart failure. "Dyssynchrony imaging" has emerged as a widely branching research area, with a multitude of publications (4–7) encompassing several methods. Characteristic of the research has been an attempt to substitute mechanical dyssynchrony for QRS duration as a selection criterion for CRT. These efforts have lately been met with skepticism despite the barrage of apparently useful tissue Doppler (velocity) imaging (TDI)-based parameters as the result of 2 key studies, the RethinQ (Resynchronization Therapy in Narrow QRS) study and the PROSPECT (Predictors of Response to CRT) study (8,9). Both studies indicated that TDI-based parameters were not useful in identifying patients who would benefit most from CRT. Technical and interpretative difficulties with current TDI-based echocardiography methods were implicated in the PROSPECT trial. In the RethinQ study, patients with narrow QRS duration, identified with echocardiography as having mechanical dyssynchrony, were randomized to CRT versus no CRT. The outcomes were similar in both groups, suggesting that TDI-based patient selection in a narrow QRS cohort may not be clinically useful.

In this regard, in this issue of *iJACC*, Oyenuga et al. (10) re-examine the issue of patient selection in heart failure patients with borderline QRS duration. They evaluated a relatively large group of CRT patients (n = 187), a significant proportion of whom had a borderline QRS duration (n = 72, mean QRS duration for this group was 115 ms). The entire cohort was subjected to extensive dyssynchrony evaluation by the use of a number of previously published dyssynchrony parameters that were applied to stored baseline images. Response to CRT was adjudicated on the basis of an improvement in ejection fraction and reverse remodeling as assessed by repeat echocardiography several months after device implant (mean 8 months).

Significantly fewer patients with a borderline QRS duration (53%) demonstrated a response to CRT compared with the wide QRS patients (75%). Interventricular dyssynchrony by pulsed-wave Doppler (interventricular mechanical delay) was more prevalent in the wide QRS compared with the borderline QRS patients (54% vs. 18%, respectively). In contrast, previously reported TDI-based indexes of intraventricular dyssynchrony (longitudinal opposing wall delay and the Yu index) were similar in both groups. Speckle tracking-based time to peak radial strain (septal to posterior wall) was noted significantly less frequently in the borderline QRS compared with the wide QRS group (47% vs. 71%, respectively). Interventricular delay and TDI-based intraventricular indexes predicted ejection fraction improvement

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only in the wide QRS group. However, septal to posterior radial strain delay by speckle tracking performed equally well in both groups, with an area under the curve of 0.79 in the wide QRS and 0.83 in the borderline QRS patients.

The results highlight and support important concepts. First, the prevalence of CRT responders increases with QRS width. Most heart failure patients with QRS duration > 150 ms have mechanical dyssynchrony, and the benefits from CRT in this population are unquestionable. Fewer patients with a QRS duration between 120 and 150 ms seem to benefit from CRT. In the large COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial (2), the primary end point was only met in the pre-defined subgroup of patients with QRS duration > 148 ms, and in the newer REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) (11) and MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) trials (12), the effect of CRT was primarily observed in patients with QRS duration > 152 and 150 ms, respectively. The multicenter RethinQ study (8) of patients with QRS duration < 130 ms, which also included only patients with echocardiographic dyssynchrony, did not meet its primary end point, and only the small pre-defined subgroup with a QRS duration between 120 and 130 ms objectively benefited from CRT. In contrast to these findings, and in accordance with the current findings by Oyenuga et al. (10), patients with a QRS duration < 120 ms have, in single-center studies on echocardiographically carefully selected patients, been shown to benefit from CRT (13,14).

Second, the character of mechanical dyssynchrony depends on QRS width. The mechanics of dilated heart failure with a very wide left bundle branch block-type QRS complex exhibits both interventricular and intraventricular dyssynchrony, whereas interventricular dyssynchrony is rare in patients with QRS duration below 130 ms. In heart failure with a more narrow QRS complex, LV wall motion homogeneities often may be related to myocardial abnormalities not related to electrical activation, which presumably are not markers for CRT response, and echocardiographic methods differ in their ability to discriminate true timing differences from these effects. Methods based on time-to-peak myocardial velocity may in this respect be less specific than strain-based methods, and the implications of the RethinQ study need to be reconsidered in this light.

Collectively, these arguments lead to the realization that QRS width to a great degree determines the potential application of echocardiographic dyssynchrony evaluation. In patients with QRS duration > 150 ms, despite the large number of studies on its predictive power in this population, echocardiographic dyssynchrony evaluation will probably play only a limited role in selecting patients for CRT. It is very difficult to improve on the large a priori chance of success in this group, and considering the impact of other factors than mechanical dyssynchrony on response, it is unlikely any echocardiographic method would add important value to patient selection. In patients with QRS duration of 120 to 150 ms, echocardiography is potentially valuable to avoid treating likely nonresponders. This strategy was followed in the CARE-HF (Cardiac Resynchronization in Heart Failure) trial (3), where patients with this QRS range had to have echocardiographic evidence of dyssynchrony to be included. Because these patients currently have a class IA indication for CRT, and the prevalence of potential responders is probably at least moderate, the echocardiographic method must be very sensitive to avoid denying treatment due to false-negative results. In patients with QRS duration < 120 ms, however, the prevalence of potential CRT responders can be expected to be low or even very low. In such a population, the accurate identification of the rare potential responder becomes all-important, and a high specificity of the echocardiographic method is imperative to avoid treating a large number of false positives.

The data from Oyenuga et al. (10) suggest that radial strain-derived mechanical delays may be an efficient way to identify such patients. This work supplements and appears to validate previous work published by this group on radial strain. If duplicated in a larger, randomized multicenter cohort, clinical application of radial strain for patient selection would be subject to some cautions. Radial strain measurement is "noisier" and therefore associated with more variability than longitudinal or circumferential strain (15,16). Selection of an appropriate sample width while applying the region of interest appears to influence timing and amplitude of radial strain. Standardization in this regard would be useful in reducing variability and consequent loss of accuracy. Multiple peaks and biphasic peaks occur often in the heart failure population, and there is no clear agreement on how best to adjudicate them. Finally, severely hypokinetic or akinetic regions have very low or absent strain, and dyssynchrony measurement may be challenging if not impossible.

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