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EDITORIAL COMMENT

Predicting Cardiac Resynchronization Response by QRS Duration

The Long and Short of It*

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As its name implies, cardiac resynchronization therapy (CRT) attempts to restore contractile coordination in hearts burdened by wall motion dyssynchrony due to conduction delay. This is achieved by stimulating the region of the ventricle with the most delayed mechanical activation so it can contract in synchrony with the earlier stimulated territory. To further assure synchrony, CRT generally employs two leads—one on the left ventricle (LV) and one on the right, pacing both simultaneously or with a small delay between them. Both acute and chronic studies have demonstrated that restoring synchrony of contraction is beneficial to the heart's performance and energetics, to patient exercise capacity and clinical well being, and to mortality from heart failure (1–7).

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One of the most critical questions to emerge from the recent clinical trial data is how should one best target this therapy; CRT devices are complex, invasive, and expensive. Repeatedly, the percentage of non-responding patients as indexed by clinical symptoms or objective evidence of the absence of reverse chamber remodeling is 25% to 30% of recipients. The major entry criteria to date have been the presence of severe dilated heart failure (New York Heart Association functional class III to IV), sinus rhythm, and evidence of a conduction delay on the electrocardiogram as reflected by widening of the QRS complex. Different studies have used entry thresholds for QRS duration ranging from >150 in the MUltisite STimulation In Cardiomyopathy (MUSTIC) trial (5), to >120 ms in the recently completed COmparison of Medical therapy, PAciNg, and defibrillatION in Chronic Heart Failure (COMPANION) trial. But what is the evidence that QRS duration identifies the right candidates?

Many acute studies have shown that the width of the QRS complex is a general correlate of mechanical response to CRT (8). This makes intuitive sense, because the level of dyssynchrony should, to some extent, be reflected in the spatially distributed electrical activation and, thus, electrocardiogram complex width. However, even under optimally controlled conditions, the correlation between QRS duration and acute response is modest—with r^2 values of 0.6, thus explaining only about 30% to 40% of the variability in contractile response to CRT. More importantly, many chronic studies have now tested the correlation between QRS duration and long-term clinical response. The latter has been assessed largely by echo-Doppler–derived objective measures of chamber function or reverse-remodeling, rather than by clinical symptoms. In general, QRS duration has been a poor predictor of the CRT response (9–11). This has been true in the larger placebo-controlled trials such as Multicenter Insync RAndomized CLinical Evaluation (MIRACLE), as well (6). Part of the issue lies in how the analysis is itself performed, that is, regression of specific outcomes against baseline QRS duration as a continuous variable, as opposed to subdividing groups into narrower (120 to 150 ms) or wider >150 ms QRS durations. But a great deal of the problem with QRS duration is that it simply does not consistently reflect the underlying level of mechanical dyssynchrony, whereas the latter increasingly appears to be most important (9,12–14).

Recent studies have demonstrated that, unlike QRS duration, the magnitude of basal mechanical dyssynchrony assessed by echocardiography or by tissue Doppler (velocity mapping) is a better predictor of outcome. Three-dimensional dyssynchrony assessed by magnetic resonance-tagged imaging was first shown to best correlate with acute mechanical benefit (8). One problem with QRS duration is that it incorporates total ventricular activation (right and left), and rapid right ventricular (RV) activation can be offset by delayed LV activation to yield a normal-range QRS despite considerable mechanical dyssynchrony. QRS widening can, in turn, reflect more diffuse conduction abnormalities or predominantly RV delays, but not belie physiologically significant LV intraventricular delay.

One of the implications of the lack of a consistent relationship between QRS duration and CRT response is that patients could well exist with narrow QRS durations yet significant mechanical dyssynchrony. Such patients would not have qualified for entry into any of the prior clinical CRT trials, yet, on the basis of recent data, might well be predicted to benefit from CRT. This hypothesis was tested by Achilli et al. (15) as reported in this issue of the *Journal*. In this study of 52 patients, 14 of them had QRS durations <120 ms, while the others had longer durations. Both groups had a similar magnitude of mechanical dyssynchrony based on wall motion/Doppler flow timing analysis. All patients received standard biventricular CRT, and were followed for a mean of one and a half years, with functional assessments made after six months. The investigators found remarkably similar clinical improvement in both groups, reduced cardiac volumes and mitral regurgitation area, and exercise capacity (6-min walk test). Basal intraventricular

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dyssynchrony did not correlate with reverse remodeling, whereas there was a weak, but significant, correlation to interventricular (RV to LV) dyssynchrony. This may reflect differences in the signal/noise levels for these measurements. There was no significant difference in these relations between the two group relations, but the correlation was not significant in the narrow QRS group, likely, in part, due to the smaller sample size and to reduced variance in the independent variable.

There are some caveats to this study. First, it was not performed in a placebo-controlled or blinded fashion, although echocardiographic analysis was performed by independent observers. Secondly, patients with both existing pacemaker-induced QRS widening and those with intrinsic conduction delay were combined. While the analysis failed to reveal any significant difference between groups, the study was not adequately powered to discern this. Given these limitations, the study sends an intriguing and important message: narrow QRS complex patients exist who benefit from CRT so long as they have dyssynchronous contraction of the LV. It further confirms that analysis of mechanical dyssynchrony is better than QRS duration for predicting this response.

Results of the PATH-CHF II study also reported in this issue of the *Journal* by Auricchio et al. (16) appear on the surface to be at odds with this conclusion, but, in reality, are not. These investigators performed a placebo-controlled crossover study of LV-only CRT. Mechanical dyssynchrony was not reported, and inclusion into the study followed standard criteria as previously used by most CRT trials. The authors raised the prospective hypothesis that QRS duration would stratify responders, and recruited equal numbers of subjects with wide complexes (>150 ms) and narrower ones (120 <QRS <150 ms). Of 86 subjects who received CRT implantation, most received a surgically implanted epicardial lead, with only 25 subjects receiving transvenous LV pacing by a coronary vein. Of these subjects, 69 completed the cross-over protocol. For the total group, LV-only pacing resulted in significant improvement in exercise performance and clinical symptoms, with positive changes correlating with the three-month period of active therapy. However, when the two subgroups were examined, only the patients in the wide QRS group showed benefits; the patients with a narrower QRS (still well within the range used in most clinical CRT trials) did not demonstrate benefits from CRT. As in prior trials, a placebo effect was observed in the quality-of-life questionnaire, as even during the inactive pacing period, quality-of-life score declined (i.e., improved symptoms) compared with baseline.

This study confirms the notion that having a particularly wide QRS complex means a greater likelihood of mechanical delay and, thus, CRT benefit. However, one should not conclude that having a QRS duration below 150 ms precludes CRT utility, as this has clearly not been demonstrated in the large-scale randomized trials such as MIRACLE or COMPANION. The pacing mode (i.e., LV-only vs. biventricular) may explain some of this difference, as LV pacing may indeed work more optimally in patients with very prolonged conduction delay times. Furthermore, this study does not reject the hypothesis that QRS by itself is adequate to optimally identify responders. Individual regression analysis was not presented, and one would not be surprised to discover considerable scatter with some responders in the narrower QRS group and nonresponders in the wide QRS group.

Finally, the study by Auricchio et al. (16) provides the largest chronic placebo-controlled data dealing with LV pacing, addressing the question whether two leads (biventricular) are really required for effective chronic CRT. Early acute studies demonstrated that both modes of pacing enhance systolic function and energetic efficiency very similarly, with, if anything, a slight advantage going to LV-only pacing (4,8,17,18). Blanc et al. (19) subsequently reported that LV-only CRT achieves similar chronic effects to that with biventricular stimulation.

The mechanisms by which LV-only pacing works remain somewhat controversial. While it was first supposed that intrinsic conduction via the functional right branch fused with the premature LV stimulation, animal and clinical studies in atrial fibrillation patients have refuted this theory (20). Rather, it appears that having early activation of the lateral wall is itself sufficient to offset the major mechanical deficits posed by left bundle branch block-type conduction delay. One study that has suggested otherwise is from Sogaard et al. (21), who reported that biventricular pacing with the LV being activated well in advance of the RV diminished CRT efficacy. This is at odds with the data using LV-only pacing, because this is the ultimate case of premature LV pacing. Further studies examining RV-LV delays are still needed to clarify this.

Should we be implementing CRT using LV-only pacing? Certainly the mode is simpler than biventricular stimulation, and could make use of traditional pacemakers. However, there is growing evidence supporting a role for internal defibrillation in many of the same patients who are CRT candidates, so this distinction becomes a bit more academic in nature. The LV lead is also the more difficult one to implant, so there are, unfortunately, no real savings in procedural time or costs. Nonetheless, this study adds fuel to the fire that either mode of treatment can work chronically.

As we advance in our understanding of the role of CRT in heart failure therapy, developments in the instrumentation, implantation methods, and stratification of appropriate candidates loom large as areas in need of clarification. QRS duration gets us into the right ballpark, but to achieve more consistent success, attention should be paid to the mechanical substrate and analysis of chamber dyssynchrony. The tools to do so exist, although none have, as yet, proven optimal or broadly applicable. Some methods, such as strain-rate tissue Doppler, are specific to equipment and unavailable in many laboratories. There remains a major

need to simplify the process and achieve a widely acceptable parameter to better stratify patients. If we stick to those with QRS durations exceeding 150 ms, we will achieve a higher responder rate, but miss many responsive candidates. Hopefully, with a usable mechanical synchrony measure, we can better select patients most likely to benefit.

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