How to predict response to cardiac resynchronization therapy?

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Online publish-ahead-of-print 24 March 2005

Cardiac resynchronization therapy (CRT) is considered a major breakthrough in the treatment of patients with end-stage heart failure.1 Initial studies demonstrated an acute improvement in haemodynamics immediately after CRT, whereas a large number of studies with mid-term follow-up (6 months to 1 year) demonstrated an improvement in heart failure symptoms, quality-of-life score, exercise capacity, and left ventricular (LV) systolic performance.1 In addition, Bradley et al.2 demonstrated in a meta-analysis, a reduced risk for heart failure death at mid-term (6 months) follow-up in patients undergoing CRT when compared with optimized medical therapy. Moreover, studies with long-term follow-up now demonstrate sustained improvement over years. In particular, Molhoek et al.3 have recently reported 125 patients undergoing CRT with up to 3 years follow-up. Besides an improvement in clinical parameters and LV systolic function, a significant reduction in hospitalization for heart failure was noted from 3.8 ± 4.9 days/year before CRT to 0.7 ± 1.6 days/year after CRT (P < 0.05). In addition, survival at 1-, 2-, and 3-year follow-up was 93, 88, and 85%, respectively. Still, 20–30% of patients do not respond to CRT, despite the use of selection criteria. According to the ACC/AHA/NASPE guidelines,4 CRT is now indicated for patients in sinus rhythm with end-stage heart failure (NYHA class III or IV), LV systolic dysfunction (LVEF < 35%), LV end-diastolic diameter > 55 mm, and QRS duration > 130 ms on the surface electrocardiogram (ECG). When these selection criteria are applied, however, 20–30% non-responders to CRT are reported consistently.5 Therefore, the search for ‘optimal and easy identification of the responder to CRT’ has attracted a lot of attention. Lecoq et al.6 elegantly evaluated 139 consecutive patients undergoing CRT, aiming at identification of responders to therapy. In line with previous studies, they identified 28% (very carefully defined) non-responders. Among clinical, 2D echo, and ECG variables, only the baseline QRS duration, the QRS duration after CRT implantation, and the shortening in QRS duration were predictive of non-response to CRT. Subsequently, multivariable analysis pointed out that shortening of QRS duration was the single best predictor of response to CRT. This observation leads us back to the value of the ECG in assessment of response to CRT. Traditionally, the QRS duration on the baseline ECG has been used to predict response to CRT, and Auricchio et al.7 demonstrated that the response to CRT was superior in patients with a QRS duration > 150 ms when compared with patients with a shorter QRS duration. At the same time, Achilli et al.8 demonstrated a substantial improvement in NYHA class and systolic LV function associated with LV reverse remodeling in patients with a QRS duration ≤ 120 ms. To determine the precise value of the baseline QRS duration, Molhoek et al.9 evaluated 61 patients and demonstrated that the baseline QRS duration was not significantly different between responders (n = 45) and non-responders (n = 16) to CRT (179 ± 30 vs. 171 ± 32 ms, NS). The same authors evaluated (similar to Lecoq et al.4) different ECG variables and concluded that the change in QRS duration immediately after CRT was the only predictor of response to CRT. The findings are of interest, because QRS shortening may now be used to assess optimal lead positioning, as pointed out by Lecoq.
et al.⁶ On the other hand, QRS shortening may not be that useful in the clinical setting, because this parameter is determined during lead implantation and ideally, selection of responders should be performed before implantation (e.g., in the outpatient clinics). Moreover, both Lecoq et al.⁶ and Molhoek et al.,⁹ demonstrated that no specific cut-off value (for QRS shortening) could be identified for actual prediction of response to CRT. Molhoek et al.⁹ showed that a reduction in QRS duration >10 ms had a high sensitivity (73%), but a low specificity (44%). In contrast, a reduction in QRS duration >50 ms had a high specificity (88%) with a poor sensitivity (18%). Using receiver operating characteristic (ROC) curve analysis, the optimal cut-off value was 30 ms, which yielded a sensitivity of 58% with a specificity of 56%.

The underlying issue is actually related to the following: it has been assumed that response to CRT was related to interventricular dyssynchrony and this is most likely reflected in the QRS duration. Indeed, Rouleau et al.¹⁰ demonstrated, using tissue Doppler imaging (TDI), that interventricular (RV vs. LV) dyssynchrony correlated well with QRS duration. These observations suggest that interventricular dyssynchrony may not be ideal to predict response to CRT, and dyssynchrony in the LV may allow more accurate prediction of response. Recent studies with TDI have shown that the relation between QRS duration and LV dyssynchrony was poor, indicating that QRS duration does not reflect LV dyssynchrony.¹¹ More recent studies have evaluated the value of dyssynchrony in the LV (intraventricular dyssynchrony) to predict response to CRT. Yu et al.¹² demonstrated that substantial LV dyssynchrony on TDI was the best predictor of LV reverse remodelling. The authors used a 12-segment model to define LV dyssynchrony. In a simplified model of four segments, a cut-off value of 65 ms was defined by ROC curve analysis to predict improvement in clinical symptoms and LV reverse remodelling.¹³ A similar cut-off value was reported by Gorcsan et al.,¹⁴ using tissue synchronization imaging, a more sophisticated form of TDI. Yu et al.¹² have subsequently demonstrated that TDI was superior over strain rate imaging for prediction of response to CRT. Despite the fact that LV dyssynchrony appears promising for prediction of response to CRT, 100% accuracy for prediction of response is not obtained. It is anticipated that other factors, such as atrial fibrillation, LV lead positioning, scar tissue in the LV target region influence response to CRT, and further research is needed to better understand response to CRT.

In conclusion, Lecoq et al.⁶ have re-emphasized that the QRS duration alone is not an accurate predictor of response to CRT. The best parameter that can be obtained from the ECG for prediction of response to CRT is the reduction in QRS duration after pacing. It is anticipated that TDI assessing LV dyssynchrony may yield optimal information to predict response to CRT.

References