Narrow QRS Is Not the Right Substrate for Cardiac Resynchronization Therapy

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The physiological underpinning for cardiac resynchronization therapy (CRT) began with Carl Wiggers in 1925. He showed that when contraction of the heart was induced by direct cardiac electric stimulation, the early phase of contraction of the heart was slowed and myocardial tension developed more gradually. Wiggers explained these findings by differences in the order of excitation of the ventricle. Subsequent studies by a number of investigators highlighted the fact that a left bundle-branch block conduction pattern was associated with dysynchronous contraction that exacerbated left ventricular systolic dysfunction. Few people appreciate the fact that Dr Morton Mower, who was involved in the development of the implantable cardioverter defibrillator, also developed the patent for cardiac resynchronization therapy in 1990 that was assigned to CPI/Guidant and subsequently licensed to Medtronic.

In 1994, Cazeau et al reported 1 patient with widened QRS and advanced heart failure who achieved marked improvement with biventricular pacing. Various short-term animal and clinical hemodynamic studies showed significant improvement in cardiac function when both right and left ventricles of a diseased heart with conduction disturbance were preexcited (biventricular pacing), and similar findings were observed recently with univentricular left ventricular stimulation in the compromised heart with conduction block. Central to all these studies was that dyssynchronous contraction associated with disturbed left ventricular conduction improved with direct left ventricular pacing.

A series of large randomized trials, including COMPANION, CARE-HF, MADIT-CRT, and RAFT, have documented the safety and efficacy of biventricular cardiac resynchronization pacing in patients with various degrees of severity of heart failure. All the studies involved patients with wide QRS complexes, with the best results observed in those with left bundle-branch block. Cardiac guideline recommendations followed in 2008, with a recent update in 2012 emphasizing the importance of wide QRS and left ventricular conduction disturbance as the best substrate for CRT efficacy.

The article by Thibault et al in Circulation involves a small randomized trial of CRT in patients with heart failure and narrow QRS (<120 ms) using exercise duration at 1 year as the primary endpoint. The Thibault trial was designed in 2002 and initiated in 2003, and it appears to be based on an observational study reported in 2003 by Achilli et al. The Achilli study enrolled patients with refractory heart failure (HF) and incomplete left bundle-branch block (narrow QRS) together with echocardiographic evidence of interventricular and intraventricular asynchrony. There were 38 patients with QRS >120 ms and 14 patients had a narrow QRS <120 ms. The CRT benefit was similar in patients with wide or narrow QRS. It should be emphasized that the authors put the word narrow in quotes (“narrow”) in the title and throughout the article when referring to QRS <120 ms because many of the patients had QRS durations <100 ms. The authors concluded that “cardiac resynchronization therapy may be helpful in patients with echocardiographic evidence of interventricular and intraventricular asynchrony and incomplete left bundle-branch block.”

It is surprising that Thibault et al. initiated their study based on limited findings in the literature, and their study did not include echocardiographic evidence of dyssynchrony. The average QRS duration was 104±9 ms, with many of the enrolled patients with QRS <100 ms. There were 12 enrolling centers, and the study ran for 8 years from 2003 to 2011 with a total enrollment of only 85 patients in the study. That means that, on average, each center enrolled <1 patient per center per year. It is surprising that the Data and Safety Monitoring Board waited 8 years to terminate the study because of futility and safety concerns.

After Thibault et al initiated their study but before publication in Circulation, there were several reports of variable CRT efficacy in heart failure patients with narrow QRS complexes. In a small observational study by Bleeker et al involving 66 studied patients with low ejection fraction and left ventricular dyssynchrony on tissue Doppler imaging, the 33 patients with QRS <120 ms had left ventricular reverse remodeling with CRT comparable with the 33 patients with QRS complex >120 ms. A larger randomized trial by Beshai et al involving 172 patients with the primary endpoint an increase in peak oxygen consumption of at least 1.0 mL per kilogram of body weight per minute during cardiopulmonary exercise testing at 6 months after randomization. The CRT-treated patients did not improve peak oxygen consumption when compared with the nontreated control group. The results of this randomized study were not very encouraging that CRT would be beneficial in patients with narrow QRS complexes.

What have we learned from the large MADIT-CRT trial regarding CRT efficacy and QRS duration? CRT was significantly more effective when the QRS duration was >150 ms than in the 130 to 149 ms range, and female patients...
were the only ones who achieved significant CRT benefit with QRS of 130 to 149 ms.\textsuperscript{18} Heart failure patients with left bundle-branch block conduction obtained excellent benefit from CRT, and there was no appreciable benefit from CRT in patients with right bundle-branch block or intraventricular conduction delay.\textsuperscript{19}

It is quite clear that CRT does not achieve a favorable result in patients with QRS durations <120 ms. On the other hand, mechanical left ventricular dyssynchrony, an important myocardial substrate for effective CRT, is exacerbated by abnormal excitation of the left ventricle with a wide QRS duration, especially when a left bundle branch conduction disturbance is present. Although many factors influence the cardiac responsiveness to CRT (lead position, type of cardiomyopathy [ischemic versus nonischemic], extent and severity of the myocardial damage, and sex), wide QRS complex and left bundle-branch block are excellent electric biomarkers for identification of heart failure patients who are likely to benefit from resynchronization therapy.

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**References**


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