Narrow QRS is not the Right Substrate for Cardiac Resynchronization Therapy

Running title: Moss; CRT and narrow QRS

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The physiologic 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 electrical stimulation, the early phase of contraction of the heart was slowed and myocardial tension developed more gradually.\(^1\) 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 dyssynchronous 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\(^2,3\) also developed the patent for cardiac resynchronization therapy in 1990\(^4\) that was assigned to CPI/Guidant and subsequently licensed to Medtronic.

In 1994, Cazeau et al. reported one patient with widened QRS and advanced heart failure who achieved dramatic improvement with biventricular pacing.\(^5\) 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),\(^6\) and similar findings were observed recently with univentricular left ventricular stimulation in the compromised heart with conduction block.\(^7\) 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,\(^8\) CARE-HF,\(^9\) MADIT-CRT,\(^10\) and RAFT\(^11\) 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,\(^12\) with a recent
update in 2012\textsuperscript{13} emphasizing the importance wide QRS and left ventricular conduction disturbance as the best substrate for CRT efficacy.

The article by Thibault et al. in this issue of \textit{Circulation} involves a small randomized trial of CRT in patients with heart failure and narrow QRS (<120ms) using exercise duration at 1 year as the primary endpoint.\textsuperscript{14} 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.\textsuperscript{15} 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 >120ms and 14 patients had a “narrow” QRS $\leq 120$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 paper when referring to QRS $\leq 120$ms since many 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”\textsuperscript{,15}

It is surprising that Thibault et al.\textsuperscript{14} 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\(\pm\)9ms 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 less than 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 this issue of
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 <120ms had left ventricular reverse remodeling with CRT comparable to the 33 patients with QRS complex ≥120ms. A larger randomized trial by Beshai et al. involved 172 patients with the primary end point 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 to the non-treated 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 ≥150ms than in the 130 to 149ms range, and female patients were the only ones who achieved significant CRT benefit with QRS of 130 to 149ms. 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.

It is quite clear that CRT does not achieve a favorable result in patients with QRS durations <120ms. 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 block conduction disturbance is present. Although many factors influence the cardiac responsiveness to CRT (lead position, type of cardiomyopathy [ischemic vs. nonischemic], extent and severity of the myocardial
damage, and gender), wide QRS complex and left bundle branch block are excellent electrical biomarkers for identification of heart failure patients who are likely to benefit from resynchronization therapy.

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**References:**


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