

Cardiac Resynchronisation Therapy in Heart Failure Patients with Narrow QRS Complex: Quo Vadis?

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Cardiac resynchronisation therapy (CRT) is an established mode of electrical therapy for advanced heart failure that is refractory to optimal drug treatment. CRT has earned its evidence-based credentials through large randomised clinical trials, which have shown significant reductions in morbidity as well as in mortality among patients with a prolonged QRS complex and moderate to severe heart failure.¹⁻⁶ The recently issued guidelines of the European Society of Cardiology (ESC) have formulated recommendations based on existing evidence and ranked as a Class IA indication the use of CRT in symptomatic heart failure patients of New York Heart Association (NYHA) classes III-IV, despite optimal pharmacological treatment, with left ventricular (LV) ejection fraction (LVEF) $\leq 35\%$, LV dilatation as evidenced by LV end-diastolic diameter > 55 mm or > 30 mm/m², normal sinus rhythm and a wide QRS complex (≥ 120 ms).⁷ The identification of suitable candidates who are anticipated to respond favourably to and benefit from CRT represents a major challenge and a prerequisite for expanding the existing indications to other patient subgroups, thus reaping the maximal possible benefit from this interventional therapy.

Cardiac resynchronisation therapy is an electrical treatment which mainly aims

to abrogate cardiac dyssynchrony. Thus, CRT is expected to be beneficial only among heart failure patients who exhibit cardiac dyssynchrony before implantation, which is evidently restored after successful CRT. A longstanding dilemma is whether we should aim at the correction of electrical or mechanical dyssynchrony *per se* regardless of QRS duration. Despite the fact that, from a pathophysiological point of view, mechanical dyssynchrony represents the ultimate target, the use of electrical conduction delay, as measured by prolonged QRS duration, is recommended in the guidelines of both the American College of Cardiology and the ESC as a consensus definition of cardiac dyssynchrony. The implementation of this current definition of dyssynchrony in clinical practice precludes the use of CRT in patients with narrow QRS by accepting *de facto* that the presence of short QRS duration denotes the absence of dyssynchrony.

The QRS complex is influenced by the vector sum of electrical activation generated by the total myocardial mass. However, time delayed myocardial segments, though lacking the critical mass to allow their "electrical representation" on the surface ECG, can still contribute to the uncoordinated and desynchronised ventricular contraction. Thus, as proposed by Aurrichio and Yu,⁸ myocardial masses of inadequate

volume to be displayed in the standard ECG may have intrinsically abnormal kinesis which can be detected by imaging modalities. This inability of the conventional surface ECG to impart the delayed electrical activation of certain myocardial segments, which nevertheless contribute to cardiac dyssynchrony, may at least partly explain the lack of association between QRS duration and mechanical dyssynchrony and the abundant evidence suggesting that a considerable percentage of patients with normal conduction exhibit ventricular dyssynchrony.⁹⁻¹¹

In this context, several studies evaluated the impact of CRT on heart failure patients without prolonged QRS duration, but with mechanical dyssynchrony defined by echocardiographic techniques, and presented evidence that CRT can also be beneficial in this subgroup of patients by improving functional class, LVEF, LV remodelling, severity of mitral regurgitation, and 6-minute walking distance.¹²⁻¹⁵ Recently, Beshai et al evaluated the same hypothesis in a prospective, double-blind, randomised, controlled clinical trial (RethinQ study).¹⁶ A total of 172 heart failure patients with a Sudden Cardiac Death in Heart Failure Trial indication for an implantable cardioverter-defibrillator,¹⁷ in NYHA functional class III, with QRS duration <130 ms and evidence of mechanical dyssynchrony as measured by echocardiography, were randomised to either CRT or no CRT. The presence of mechanical dyssynchrony was identified using echocardiographic imaging methods. In 96% of cases the tissue Doppler-defined presence of an opposing wall delay ≥ 65 ms was used as a qualifying criterion,¹⁸ while the remaining 4% of patients exhibited a significant mechanical delay in the septal to posterior wall, obtained by M-mode in the parasternal long-axis view.¹⁹ After 6 months, among 156 patients assessed (76 in the CRT and 80 in the control group), CRT was not shown to confer any benefit in patients with QRS duration <120 ms, as evidenced by lack of improvement in peak oxygen consumption.

Obviously, the study by Beshai et al raises important questions whose clinical implications may have an effect on everyday clinical practice. Could the neutral effect of CRT be attributed to an inherent inability of this therapeutic intervention to ameliorate the status of heart failure patients without electrical conduction delay? Are these results a consequence of the well known methodological issues related to the imaging methods used to identify mechanical dyssynchrony?²⁰ It is rather difficult to answer these questions, but there are indeed some areas of uncertainty

in the study that could at least partly explain the lack of benefit in the CRT group.

A critical appraisal of the study with a view to evaluating the reported negative findings should primarily be focused on the type of imaging method used as an inclusion criterion and as an index of cardiac dyssynchrony. The authors reported that the tissue Doppler criterion lacks specificity and may have accounted for the neutral effects of CRT. These limitations are also verified by the PROSPECT trial, which demonstrated that the echo index that was primarily used in the RethinQ trial (delay between time to peak systolic velocity at basal septal and basal lateral segments) has low sensitivity and specificity and cannot improve the selection of patients for CRT implantation.²¹ Recent data suggest that a combined echocardiographic assessment of longitudinal dyssynchrony by tissue Doppler imaging and radial dyssynchrony by speckle-tracking strain can predict the functional response to CRT better than either technique alone.²² On the other hand, these concerns are being raised after the completion of the study analysis, whereas the method of echo measurement of dyssynchrony implemented in the RethinQ study was the one most supported by the existing evidence in the literature when the study was designed.²³

Furthermore, the authors do not report data regarding post-implantation cardiac resynchronisation and reduction of pre-implantation dyssynchrony, either at the 14-day evaluation or at the 6-month follow-up, despite the fact that an echo assessment was performed. Thus, we are unaware whether the baseline mechanical dyssynchrony was indeed corrected by the implemented interventions and whether the lack of beneficial effect afforded by CRT might be associated with an inability to reverse the initial enrolling feature of cardiac dyssynchrony. It is noteworthy that the reduction of LV dyssynchrony acutely after CRT has recently been shown to be predictive of mid-term response.²⁴ However, and in contrast to the accumulating evidence, most CRT studies do not provide data on restoration of both electrical and mechanical dyssynchrony after implantation. Unfortunately, the vast majority of CRT studies, including the one by Beshai et al, consider the implantation of a biventricular pacing system successful when the patient leaves the hospital with a functioning electrode placed inside a coronary sinus branch. According to the recently published study by Bleeker et al,²⁴ which is in agreement with our own experience, selection of an appropriate coronary sinus tributary and post-im-

plantation echocardiography-guided optimisation of CRT parameters are of the utmost importance in order to achieve resynchronisation and clinical benefit. Taking into consideration that CRT aims principally at resynchronising the ventricles, and not just changing the depolarisation pattern, we are justified in demanding these data from studies that may heavily influence our practice.

In the RethinQ study the QRS duration was one of the inclusion criteria that had to be met in the screening evaluation. Furthermore, the accurate measurement of QRS duration was of primary importance, not only for the exclusion of patients with a QRS >130 ms, but also for the proper patient randomisation, which was performed in blocks stratified by widest QRS duration (<120 or \geq 120 ms) measured at the time of enrolment.²³ However, the authors do not report the specific mode of ECG evaluation that was implemented in the screening process. We have previously demonstrated the presence of significant interobserver variability in QRS measurement, as well as significant discrepancies in QRS duration measurement depending on the type of method used (conventional measurement of maximal QRS duration in the 12-lead ECG, versus on-screen measurement of computer-based ECG using digital callipers, versus total ventricular activation using signal-averaged electrocardiography).²⁵ These parameters are rarely taken into account and may partly explain the inconsistent association of QRS duration with cardiac dyssynchrony and the heterogeneity of methods that have been used in the selection of candidates for CRT therapy.²⁰

Finally, the negative findings of the study may be attributed to the relatively inadequate statistical power of the trial. The RethinQ population included heart failure patients with a narrow QRS, the latter denoting a more favourable prognosis and a lower all-cause mortality rate compared to patients with a prolonged QRS.²⁶ It is well known that the benefit conferred by a therapeutic intervention is related to the level of risk of the target patient population. Thus, the population size of 172 patients (156 patients finally assessed at 6 months) may represent a rather inadequate power for estimating a subtle treatment effect in a relatively low-risk heart failure patient subpopulation, while the sample size calculation is based on a rather arbitrarily pre-specified difference of 23% in the proportion of patients who achieved the primary endpoint in the CRT group, as compared with the control group. Finally, the authors limited their evaluation of clinical improvement to the

assessment of peak oxygen consumption at the 6-month follow-up examination and found no difference: however, NYHA class did improve in the CRT group ($p=0.006$). Furthermore, the subgroup with a QRS duration of 120-130 ms did benefit from CRT. All these inconsistencies, the methods employed to define dyssynchrony, and the small number of the study participants, cast certain doubts as to the validity and general applicability of the findings and conclusions of the RethinQ trial.

The above mentioned issues strongly support the notion that further large-scale, prospective, adequately powered, double-blind trials are needed in order to delineate the potential beneficial effect of CRT on the subpopulation of heart failure patients with narrow QRS, as well as the optimal echocardiographic imaging method for enabling the most accurate definition of cardiac dyssynchrony and the selection of responders. Meanwhile, we should follow the recently published guidelines of the ESC and European Heart Rhythm Association by routinely excluding patients with narrow QRS from CRT. However, we should keep in mind that further insight into this issue is still warranted and the currently existing evidence, including the study by Beshai and co-workers, is inconclusive. This study mostly reflects the currently existing methodological limitations on theoretical and practical issues related to successful CRT, and thus should be interpreted in the context of its main limitations.

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