EDITORIAL

Beyond the measurement of QRS complex toward mechanical dyssynchrony: cardiac resynchronisation therapy in heart failure patients with a normal QRS duration

A Auricchio, C M Yu

Mechanical systolic dyssynchrony exists in many patients with heart failure, irrespective of QRS duration, and so more patients may derive benefit from cardiac resynchronisation therapy than previously considered

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Cardiac resynchronisation therapy (CRT), a novel treatment for symptomatic patients with severe heart failure and ventricular conduction delay, resynchronises left–right ventricular contractions and wall motion within the left ventricle, and also maximises preload by shortening the atrioventricular delay.^{1–3} CRT provides symptomatic benefit,^{4–5} induces reverse remodelling,^{6–8} and reduces hospitalisations and mortality.⁹ CRT is indicated in patients with severe symptomatic heart failure, refractory to medical treatment, and QRS duration of more than 130 ms.¹⁰ However, there is increasing evidence that CRT may be beneficial in patients with normal QRS duration but with some degree of interventricular and intraventricular delay.^{11–12}

Studies addressing this issue are small, non-controlled, non-randomised, and use different definitions of mechanical delay, but the results appear consistent. If the findings are going to be confirmed in large prospectively controlled trials, then we shall review several pathophysiological concepts related to ventricular conduction delay and its haemodynamic and mechanical consequences.

QRS DURATION IS AN INADEQUATE INDICATOR OF MECHANICAL DYSSYNCHRONY

The use of QRS duration has been generally regarded as a good parameter describing asynchrony, and its value resides in the large scale use of ECG and in its clinical simplicity. Acute data have demonstrated that patients with a QRS duration between 120–150 ms have less increase or no change in cardiac contractility and stroke volume compared to patients with a QRS duration longer than 150 ms. While short term (three months) results suggested a negative trend in patients with QRS duration between 120–150 ms with little or no improvements in exercise capacity and quality of life,¹³ one year data have surprisingly showed a significant increase and near comparable treatment effect in this patient population, compared to patients with QRS duration longer than 150 ms.¹⁴

There are two further observations that have raised concerns over the real value of the QRS duration in predicting mechanical dyssynchrony (or mechanical asynchrony): (1) during atrial sensed sequential left ventricular pacing alone, the QRS duration is usually longer than during intrinsic QRS (left bundle branch block (LBBB)) which contrasted with a significant increase of left ventricular contractility and improvement of stroke volume; (2) QRS shortening during simultaneous right and left ventricular pacing does usually not correlate with clinical efficacy of CRT. Together these findings question the extent to which QRS duration is linked to mechanical dyssynchrony; notably, recent animal studies using tagged magnetic resonance imaging have further shown the dissociation that exists between electrical delay times and mechanical dyssynchrony.¹⁵ However, other possible explanations for this apparent dissociation may exist. First of all, the cut-off for defining certain abnormal QRS duration may be more arbitrary than so far accepted, and probably we may have to consider once again vectocardiography or signal averaging ECG for more precise definition of QRS duration. Also adjusting the QRS complex duration to the degree of ventricular dilatation may be important. Second, QRS complex results from the vectorial sum of electrical phenomena generated by myocardial masses over time. Thus, a myocardial mass which is timely delayed can influence the QRS morphology and duration only if it has substantial volume. Minor regional and local changes in mass, electrically represented by a small vector, may not be adequately displayed in the standard ECG. However, such small masses may have enough volume or intrinsic abnormal kinesis to be detected by imaging techniques.

HIDDEN ELECTRICAL ABNORMALITY CAUSES MECHANICAL ABNORMALITY

Myocardial Purkinje cells build a diffuse network and propagate electrical impulses at high velocity in a uniform manner from the endocardium to the epicardium. In a region of myocardial disease, rearrangement of extracellular matrix and of working myocytes results in intramural disarray which may influence the entry, the direction, and ultimately the velocity of propagation of conducting impulse within diseased area.

Abbreviations: CRT, cardiac resynchronisation therapy; LBBB, left bundle branch block; TDI, tissue Doppler imaging

See end of article for authors' affiliations

Correspondence to:
Dr Angelo Auricchio,
Division of Cardiology,
University Hospital,
Leipziger Strasse 44,
D-39120 Magdeburg,
Germany; angelo.
auricchio@medizin.
uni-magdeburg.de

In an animal model of LBBB, difference in regional (septum and lateral wall) as well as transmural protein and gene expression of hypertrophy has been demonstrated.¹⁶ This indicates that, because of changes in activation sequence following the onset of LBBB, abnormal regional loading conditions are generated which induce different degrees of hypertrophy. It is hypothesised that in abnormal activation sequence, the physiological endocardium to epicardium depolarisation gradient is lost and is replaced by a diffuse activation wave front travelling throughout the myocardial wall; this is strongly supported by recent electrophysiological mapping data.¹⁷ The disorganised electrical depolarisation creates local (endocardium, myocardium, and epicardium) abnormal loading conditions, thus favouring different degrees of transmural hypertrophy. Following this reasoning, in the diseased ventricle there may be large difference in hypertrophy and myocyte function, which could be detected from tissue Doppler imaging (TDI). The sensitivity of TDI to detect very early stage myocardial dysfunction before the occurrence of hypertrophy has recently been demonstrated in different forms of cardiomyopathy.^{18–21}

MEASUREMENTS OF MECHANICAL ASYNCHRONY

By focusing on measurement of mechanical dyssynchrony, the important questions are: (1) whether to assess inter- or intraventricular mechanical asynchrony; (2) whether to examine systolic or diastolic dyssynchrony; (3) how to define the range of normality in heart failure patients; and, very importantly, (4) whether the selected parameter(s) of dyssynchrony predicts response to CRT.

A few non-invasive imaging techniques could be employed for the assessment of mechanical dyssynchrony. These include radionuclide imaging, magnetic resonance imaging, echocardiography, and TDI. Radionuclide imaging has been shown to be useful to assess interventricular dyssynchrony,²² though the spatial and temporal resolutions are limited and a detailed evaluation of interventricular dyssynchrony may not be possible. Cardiac magnetic resonance imaging is a relatively luxurious investigation that is potentially useful to quantify regional wall motion and strain rate when combined with tagging technique, though further tests are needed to evaluate such a role. Echocardiography is therefore offering a practical tool which has solved most of the aforementioned limitations of other imaging techniques.

In patients with heart failure and ventricular conduction delay, two different levels of ventricular asynchrony by echocardiography have been recognised: interventricular and intraventricular delay. At the present time, it is still a matter of debate which of these two delays plays a major role in depressing ventricular performance.

Interventricular and intraventricular dyssynchrony can be easily and routinely assessed by conventional Doppler echocardiography. Interventricular delay is usually defined as the time difference between the onset of aortic flow and the onset of pulmonary arterial flow in respect to the beginning of the QRS complex. A delay greater than 40 ms is considered compatible with significant dyssynchrony. Because the time to ejection of the right and left ventricle could be influenced by several factors, the predictive utility of interventricular delay has been questioned.

Intraventricular dyssynchrony is considered by the vast majority of researchers to be the most important aspect of delay which is targeted by CRT. Intraventricular delay may be defined as the mechanical dispersion of motion within the left ventricle. This can be assessed in various ways. The method proposed by Pitzalis and colleagues is a simple one but has only been employed exclusively in patients with very long QRS duration where the timing of isovolumic contraction of the anterior septum is compared to the contraction of

the posterior wall during the ejection phase.²³ Furthermore, this method, as for many other echocardiographic criteria, has never been prospectively tested in large populations, thus the sensitivity, specificity and predictive values are unknown. Regional systolic and diastolic synchronicity can be evaluated by TDI comparing the time to peak systolic contraction and early diastolic relaxation of multiple segments, and therefore offers a comprehensive assessment of cardiac synchronicity.

Improvement of interventricular dyssynchrony after CRT has been demonstrated by TDI in a previous study.²⁴ However, TDI parameters of interventricular delay have not been shown to predict the improvement of cardiac function.²⁵ This is likely explained by the fact that the magnitude of pre-pacing interventricular delay is relatively small when compared with intraventricular dyssynchrony; the peak right ventricular contraction is later than the left ventricle physiologically (lower pressure chamber in the right ventricle); and, conceptually, correction of intraventricular delay will simultaneously improve interventricular delay through ventricular interdependence. A number of parameters based on TDI have been proposed to evaluate intraventricular dyssynchrony. These parameters either examine the time to peak myocardial systolic contraction (Ts) between two or multiple segments, or the dispersion of Ts by calculating the standard deviation of Ts of multiple segments in the left ventricle, typically 12 (Ts-SD).^{24–25} Mechanical delay in the left ventricular free wall has been speculated in patients with LBBB since CRT is gaining acceptance. On mechanical perspective, delay in Ts in the lateral wall has been observed only when TDI was employed to examine regional wall motion, which is corrected acutely and during intermediate term follow up.^{26–27} Interestingly, a large value of Ts-SD signifying more severe dispersion of regional Ts has been shown to strongly predict responders of reverse remodeling.²⁵ Other proposed indices of systolic dyssynchrony include counting the number of segments with post-systolic shortening and possibly strain rate parameters. The former parameter has been observed to correlate with the beneficial change in systolic function.²⁸ However, a recent comprehensive analysis suggested that assessment of Ts-SD is the best predictor of reverse remodelling.²⁹ This may shed some light into the selection of suitable parameters of mechanical dyssynchrony in future studies.

MEASUREMENTS OF MECHANICAL ASYNCHRONY IN LESS WIDE AND NORMAL QRS HEART FAILURE

The wealth of knowledge on mechanical asynchrony in patients with less wide and narrow QRS duration is scarce. While mechanical asynchrony is a consistent (but not exclusive) observation in patients with LBBB who had wide QRS duration, this phenomenon is less common in patients with less severe or even an absence of electrical dispersion on ECG. In a recent study, the prevalence of responders of reverse remodelling was lower in patients with a QRS duration of 120–150 ms, which was attributed to the less severe mechanical asynchrony as reflected by a lower Ts-SD.³⁰ In order to explore the potential role of CRT in heart failure patients with narrow QRS duration (< 120 ms), it is imperative to examine whether mechanical dyssynchrony exists in such patients. Intriguingly, TDI analysis showed that there was objective evidence of mechanical dyssynchrony in nearly half of heart failure patients with normal QRS duration (fig 1).³¹ This finding supports the view that CRT may potentially be beneficial to target heart failure patients who had accompanied features of mechanical dyssynchrony. This hypothesis will be partly examined by two multicentre clinical studies: the CARE-HF and PROSPECT studies.

Figure 1 Comparison of the standard deviation of the time to peak myocardial systolic contraction of the 12 left ventricular segments (Ts-SD) in the normal controls, heart failure (HF) patients with normal QRS duration (120 ms), and heart failure patients with wide QRS duration (> 120 ms). * $p < 0.001$ v controls, ** $p < 0.001$ v controls and v HF with QRS (120 ms).

CONCLUSIONS

Mechanical systolic dyssynchrony exists in many patients with heart failure irrespective of QRS duration. Although mechanical dyssynchrony is more prevalent in patients with longer QRS group, it is not uncommon in patients with normal QRS, estimated at around 50%. Small, non-controlled trials have shown symptomatic and echocardiographic improvements of patients with moderate to severe heart failure and less wide QRS, generating excitement about the possibility that more patients may benefit from CRT. Theoretical considerations may indeed support the applicability of CRT in heart failure patients with normal QRS duration. Larger controlled, randomised studies are needed, as well as improved understanding of which parameters of mechanical asynchrony better describe this condition.

Authors' affiliations

A Auricchio, Division of Cardiology, University Hospital Magdeburg, Germany

C M Yu, Division of Cardiology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong

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