Can real-time three-dimensional echocardiography be used reliably for the assessment of left ventricular dyssynchrony?

Est-ce que l’échographie tridimensionnelle peut être utilisée de façon fiable dans l’évaluation d’un asynchronisme ventriculaire gauche?

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KEYWORDS

Biventricular pacing; Three-dimensional echocardiography; Dyssynchrony

Abbreviations

CRT cardiac resynchronization therapy
LV left ventricle/ventricular
LVEF left ventricular ejection fraction
RT3DE real-time three-dimensional echocardiography
SDI systolic dyssynchrony index
TDI tissue Doppler imaging

The assessment of LV dyssynchrony through a variety of advanced imaging modalities has garnered substantial interest, as current dyssynchrony markers remain equivocal for predicting response to CRT in patients with advanced heart failure. Current recommendations support the use of CRT in symptomatic patients with moderate-to-severe heart failure, New York Heart Association functional class III or IV, QRS duration greater or equal 120 ms and an ejection fraction less or equal to 35%, who have been optimized with medical therapy. This device-based therapy has important therapeutic benefits, including functional and clinical

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improvements, significant reverse LV remodelling and an increase in ejection fraction on echocardiography, and most importantly, improved survival. QRS duration is an electrical surrogate for dyssynchrony and is the current standard variable used for patient selection; however, the 30–40% non-responder rate underscores the need for a more powerful and specific criterion for mechanical dyssynchrony. A better understanding of device-related factors that may affect post-implantation response directly is also required. Although no echocardiographic dyssynchrony variable to date can predict response more accurately than or supplant the current selection criteria, the role of imaging for CRT candidates is gaining momentum rapidly, and the successful development and validation of newer modalities for assessing dyssynchrony will have a great impact on future clinical practice.

Colour TDI assessment of LV dyssynchrony is the most extensively studied echocardiographic method and a number of established TDI criteria have been shown in small studies to be highly predictive for CRT response. Well-known TDI velocity-based indices include the Yu index, which is the standard deviation of time-to-peak systolic velocity of 12 LV segments, and the Bax index, which analyses velocity delay between the four basal segments in the longitudinal plane \(r^2=0.5\). Despite good experience with this two-dimensional application, TDI has a number of limitations, including an angle-dependency that permits assessment of timing of motion in the longitudinal plane only, an inability to differentiate between passive motion or tethering and active motion, and non-simultaneous assessment of different LV segments. The focus on longitudinal assessment with TDI creates a significant disadvantage, as this is an incomplete LV motion analysis and is subject to greater variability. Furthermore, when a variety of TDI variables were tested with high-quality control in the large, prospective, multicentre predictors of response to CRT (PROSPECT) study, they were found to have only modest specificity and sensitivity for predicting clinical response or reverse LV remodelling. The conclusions from the study were that TDI methods can be technically challenging and poorly reproducible and can yield equivocal results when attempted widely. In addition, TDI dyssynchrony variables have not been advantageous for proving benefit with CRT in specific heart failure populations, such as in patients with narrow QRS width. Newer imaging methods may offer insight into the complex relationship of electromechanical delay in this group.

To overcome the limitations of TDI, RT3DE has emerged as a newer method that offers a comprehensive and simultaneous assessment of intraventricular dyssynchrony. In this issue of Archives of Cardiovascular Diseases, Deplagne et al. describe in a small, prospective study how three-dimensional assessment of ventricular dyssynchrony can provide additional benefit to two-dimensional dyssynchrony assessment in predicting response with biventricular pacing [3]. This study, like others, capitalizes on the potential advantages of RT3DE. Three-dimensional dynamics of the entire LV, with angle-independent information about radial, circumferential and longitudinal timing, can be obtained in a single recording with this method. Resynchronization, improvement in ejection fraction and a reduction in LV end-systolic volume, which is better for predicting improved survival with CRT [4], can also be assessed quickly and repeatedly with RT3DE during long-term follow-up. Indeed, RT3DE offers accurate ejection fraction and volumes estimations that are similar to magnetic resonance imaging and better than two-dimensional imaging. Potential disadvantages of this method are related largely to its novelty and ongoing development. Concerns over poor image quality and low frame rates with RT3DE, the potential for disagreement and imperfect translation between multiple software systems used for three-dimensional analysis, the conflicting results of validation studies and the lack of clearly established normal values still need to be resolved.

RT3DE dyssynchrony assessment is performed by tracing endocardial borders manually to create a three-dimensional reconstruction or “shell” of the LV. This LV model is then subdivided into 16 or 17 volumetric segments and the volume changes in each segment are calculated throughout the cardiac cycle. The dispersion in the times to minimum systolic volume attainment for each segment is taken and then superimposed as time—volume curves. Synchronous contraction implies that most segments will achieve minimum volume at the same time point in the cardiac cycle, and thus the time—volume curves for each region will be aligned. In a patient with significant dyssynchrony, the time points, depicted by the curves, will appear non-uniform and misaligned. Kapetanakis et al. developed a SDI (the standard deviation of the 16 segments’ time to minimum systolic volume attainment, expressed as a percentage of the cardiac cycle) to calculate the degree of global LV dyssynchrony [5]. A higher SDI indicates greater intraventricular dyssynchrony, although cut-off values for significant dyssynchrony to predict CRT response are yet to be determined. The methodology of RT3DE has been advanced by new software algorithms designed to improve the delineation of LV borders, in order to minimize errors and the introduction of artefacts from the manual correction of the endocardial boundary. In addition, colour-coded parametric imaging is applied to the three-dimensional data to reveal maximum dyssynchrony between the areas of early and latest activation. These displays are highly intuitive, and desirable from an electrophysiologist’s perspective, to help guide lead placement that is concordant with the site of latest mechanical activation.

Current normal values have been proposed in several small studies and are notably different. This may be explained in part by whether the LV segmentation model in these studies includes the apical cap, irrespective of whether this segmentation model is defined as having 16 or 17 segments. Kapetanakis et al. set out to define the dyssynchrony index in normal patients (mean SDI 3.5 ± 1.8%, with an arbitrary cut-off for dyssynchrony greater than three standard deviations above this mean, or 8.3%) in a 16-segment model in which the apical cap was included and divided among four apical segments. This study proved that significant differences in the SDI exist between groups with mild, moderate and severe LV dysfunction. SDI correlated in a strong logarithmic fashion with worsening LVEF, independent of QRS duration, and was significantly higher in responders to CRT compared with non-responders [5]. The negative correlation between the dyssynchrony index and LVEF, irrespective of QRS width, has been confirmed by another study \(r = -0.91\), which also sought to define an abnormality threshold for dyssynchrony in patients with
dilated cardiomyopathy, with and without left bundle branch block, across a wide range of ages. The abnormality threshold here was lower than in the study by Kapetanakis et al. and was defined as 4.0% (mean plus two standard deviations of the normal controls) in a 16-segment model that excluded the apical cap entirely. This threshold was also found to be age- and sex-independent [6]. Furthermore, a different group of investigators found that a cut-off SDI of 5.6% had a moderately high sensitivity and specificity for predicting acute improvement in LV volumes with CRT [7]. Deplagne et al. quantified the SDI as the standard deviation of 17 segments and showed that the three-dimensional SDI was significantly higher in responders compared with non-responders, although echocardiographic response here was defined by a 10% reduction in LV end-systolic volume and not 15% as in other studies. Significant improvement in this index occurred after device implantation and interventricular delay optimization, although this trend was not exploited further to derive normal values or a cut-off value for predicting CRT response.

For this method to gain acceptance, larger multicentre studies are needed to define normal values and an abnormal threshold that can identify candidates for CRT reliably. The discrepancy between using a 16-segment model (without apical cap) and 17-segment model (with apical cap) for dyssynchrony assessment also warrants clarification. The apical cap, which is used mainly in perfusion analysis, contributes little to overall ejection fraction and has minimal endocardial excursion, which can make measurement of time to minimum volume difficult in this region. Including the apex may therefore confound dyssynchrony analysis, making a 17-segment model less specific and less preferable than a 16-segment model that excludes the apical cap [6]. On a similar theme is the issue of how to incorporate dyskineic or akinetic areas in the dyssynchrony analysis, as we must first understand how such segments can shift the SDI and affect the accuracy of this method. A "weighted" SDI that places higher value on viable segments, and on regions that contribute the most towards systolic performance (i.e. the basal segments), may be a more rational way of quantifying dyssynchrony.

Because most experience is with TDI, and because several TDI variables have been related to favourable response, studies comparing RT3DE with TDI have sought to validate this newer technique. Kapetanakis et al. found only a moderate correlation ($r = 0.38$) between RT3DE and TDI for all patients when using the SDI cut-off value of 8.3% for significant dyssynchrony. Burgess et al. found similar results in 100 patients with ischaemic cardiomyopathy, with a poor correlation ($r = 0.11$) between RT3DE and TDI dyssynchrony assessment in a 12-segment model, although they used the same SDI cut-off of 8.3% defined previously by Kapetanakis et al. [8]. This study showed that RT3DE identified a smaller number of patients with dyssynchrony than TDI, but perhaps a cut-off value of 8.3%, with its specificity of 100% but sensitivity of only 46%, may be too high to apply to a normal population [7]. In contrast to the findings by Kapetanakis et al. and Burgess et al., other studies have shown a fair degree of correlation between TDI and RT3DE. Multiple RT3DE dyssynchrony indices, including time to minimum systolic volume for 6-, 12- and 16-segment models, were shown in a study of 122 patients by Takeuchi et al. to have good correlation ($r = 0.71$) and a concordance rate of 79% with a TDI index of dyssynchrony, specifically the standard deviation of time to peak systolic velocity of 12LV segments. Correlation between RT3DE and TDI improved when a larger number of segments, such as in the 16-segment model, were used [9]. When RT3DE was compared with phase analysis of single photon emission computed tomography perfusion for dyssynchrony quantification in a small number of patients, a good correlation ($r = 0.80$) was observed [10]. Studies have produced conflicting results for validation of RT3DE, but it should be emphasized that without a gold standard and a clear cut-off value for SDI, proper comparison between methods may not be possible. Furthermore, poor correlation between these methods is not entirely surprising, as TDI and RT3DE evaluate dyssynchrony in different directional planes and focus on distinct systolic indices and timings, with TDI evaluating peak tissue velocities in early systole and RT3DE evaluating minimum volumes as an expression of endocardial excursion in end systole. Few studies such as the one by Deplagne et al. have directly compared RT3DE and TDI indices of dyssynchrony for predicting clinical response and reverse remodelling after CRT, which is after all one of the more meaningful questions for understanding the true merit of RT3DE.

There are several technical considerations for improving the use of RT3DE. Endocardial tracking, the first step towards creating a three-dimensional shell, depends on excellent imaging resolution. Improved imaging transducers are needed to produce high image quality and avert the need for manual adjustments of border contours. Deplagne et al. acknowledge the difficulty of endocardial tracking in patients with poor ultrasonic windows. The authors also mention the drawbacks of using different imaging machines for making two-dimensional and three-dimensional dyssynchrony measurements. This could affect comparisons between modalities, particularly in studies with a small number of subjects. We agree with these authors that good interobserver agreement and reproducibility of RT3DE dyssynchrony measurements across echocardiography laboratories need to be confirmed before confidence in this method is gained and implementation can occur.

RT3DE is a promising advanced imaging modality for dyssynchrony assessment and for accurate evaluation of LV reverse remodelling with CRT. Rigorous validation of RT3DE and the clear establishment of cut-off values are needed before we can implement this technology and potentially improve the practice of selecting patients for CRT.

References


