New Approaches to Evaluate Mechanical Dyssynchrony – Potential Usefulness in Predicting Response to Cardiac Resynchronization Therapy

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Cardiac resynchronization therapy (CRT) is an established therapy for patients with advanced heart failure and wide QRS intervals. Numerous single-center studies indicated that the assessment of mechanical dyssynchrony helps predict response to CRT. However, two multi-center studies disprove the idea that the conventional assessment of mechanical dyssynchrony is useful for CRT patient selection. The purpose of this review is to provide an overview of the conventional methods as well as three novel approaches (cross-correlation analysis, Fourier analysis of strain uniformity, and discoordination analysis) for dyssynchrony assessments and their potential usefulness in predicting response to CRT.

Key Words: Cardiac resynchronization therapy • Dyssynchrony • Echocardiography

INTRODUCTION

Cardiac resynchronization therapy (CRT) is an established treatment for patients with advanced heart failure (HF) and wide QRS intervals (> 0.12 sec).1,2 CRT improves cardiac function and clinical symptoms and reduces mortality.3-8 However, despite its overall efficacy, 30% to 40% patients receiving CRT do not benefit from the therapy, and one concern is that patient selection, which has been based on a wide QRS duration, inadequately identifies mechanical dyssynchrony.8-12 It has been proposed that mechanical dyssynchrony rather than electrical dyssynchrony better predicts response to CRT.8-10,12-14

Mechanical dyssynchrony assessment: conventional steps and its limitations

Mechanical dyssynchrony, the difference in regional contraction timing, is usually a consequence of electrical dyssynchrony due to ventricular conduction delay or right ventricular pacing.8-15 Data from single-center studies suggests that numerous parameters of mechanical dyssynchrony can improve patient selection for CRT on the top of a wide QRS duration.8-10,12-14 These parameters include the septal-to-posterior wall motion delay on M-mode echocardiography (> 130 ms), anteroseptal-to-posterior wall delay using speckle tracking radial strain (> 130 ms) and several indices based on tissue Doppler imaging (TDI), such as septal to lateral delay (SLD) in apical 4-chamber view (> 60 ms), maximum difference in opposing wall delay (MD) in apical 4-chamber or long-axis views (> 65 ms) and the standard deviation of 12 sites (TsSD) using longitudinal tissue Doppler velocities (> 34 ms).8-10,12,16-19

However, recent two multi-center prospective studies disprove the idea that the assessment of mechanical dyssynchrony is useful for CRT patient selection. The
Predictors of Response to CRT (PROSPECT) trial prospectively evaluated the value of 12 echocardiographic metrics of mechanical dyssynchrony to predict response to CRT, based on both conventional and TDI-based methods, in 426 patients with HF and a standard indication for CRT from 53 medical centers. Given the modest sensitivity and specificity in this trial, no echocardiographic measure of dyssynchrony could be recommended to improve patient selection for CRT beyond current guidelines. Likewise, the Resynchronization Therapy in Patients with HF and Narrow QRS (RethinQ) trial showed that patients with a QRS duration < 130 ms and evidence of mechanical dyssynchrony, primarily based on TDI measures, did not benefit from CRT.

In view of the two negative studies of mechanical dyssynchrony, we are faced with a paradox. On one side, numerous single-center studies indicated that the assessment of mechanical dyssynchrony helps predict response to CRT. On the other side, randomized multi-center trials showed contradictory results. Although many studies have been done to quantify mechanical dyssynchrony in hopes of refining patient selection, there is still no ideal dyssynchrony parameter that can be used to recommend whether a patient should undergo CRT. Many experts believe that techniques to quantify mechanical dyssynchrony need to be refined, not abandoned, and will play a role in selecting patients for CRT in the future.

To realize the limitations of mechanical dyssynchrony, it is necessary to know why mechanical dyssynchrony might occur and how we measure it. In normal subjects, the left ventricle is activated almost simultaneously through the rapid conduction system, and this is followed by synchronous contraction. Patients who have left bundle branch block or other ventricular conduction disturbances have a markedly different activation sequence. Patients with left bundle branch block, the inter-ventricular septum and right ventricle are activated early, whereas the posterior and lateral left ventricular (LV) walls are activated late. The time difference in activation leads to early septal and late posterior-lateral contraction. Early septal contraction causes posterior-lateral thinning or stretching, followed by late posterior-lateral contraction causing septal thinning or stretching. This asynchronous contraction generates heterogeneous strain and stress in the left ventricle and results in inefficient LV performance. CRT can reverse the adverse consequences of asynchronous activation by stimulating the right ventricle and left ventricle simultaneously or pacing the left ventricle only.

The conventional steps for quantifying mechanical dyssynchrony are as follows. First, curves to depict the motion or deformation of ≥ 2 segments of the left ventricle (velocity, strain or strain rate) are determined from TDI or speckle tracking echocardiography. Second, the time from a reference point on electrocardiogram to a peak of velocity or strain is measured for each curve. Finally, mechanical dyssynchrony is quantified from the dispersion of the time-to-peak values (the difference or the standard deviation). Although fast and easy to measure, time-to-peak analysis that uses only a single data point of the velocity or strain curve is methodologically simplistic and likely susceptible to noise and technical factors. Recent studies including the PROSPECT trial have shown that time-to-peak analysis is highly observer-dependent and poorly reproducible, even in normal controls. Peak systolic velocities from TDI are often difficult to locate in cases of multiple peaks, a flat velocity contour, marked beat-to-beat variations and no positive velocity during systole. Another issue is that TDI measures motion relative to the transducer, whether active or passive. The failing heart may show a rocking movement that is difficult to interpret the data and that the measured value may not really represent asynchronous contraction.

Most of mechanical dyssynchrony analyses only assess the time differences of mechanical activity in different regions and do not consider the magnitude of regional contraction. Therefore, such analysis is unable to clarify whether the measured value truly reflects a temporal delay in mechanical contraction due to asynchronous activation or the heterogeneity of LV contraction in the wall. The former is a likely target for CRT, whereas for the latter, the role of CRT is not clear.

**Cross-correlation analysis of dyssynchrony**

Fornwalt et al. developed a new parameter, cross-correlation delay (XCD), to measure dyssynchrony throughout the cardiac cycles. XCD uses a signal processing method called a cross-correlation analysis that utilizes all velocity data from 3 consecutive beats. The analysis is computed between two tissue velocity curves by shifting one curve in relation to the other along the
time axis and computing the correlation coefficient between the two curves for each time shift. A cross-correlation coefficient value of 1 indicates that the two curves are completely synchronous in time, whereas a value of 0 indicates that there is no correlation between the two curves. The time shift that results in the maximum correlation coefficient is the temporal delay (Figure 1). The advantage of XCD is that the analysis does not require identification of ejection phase or manual selection of peak systolic velocities.

Fornwalt et al. compared the ability of XCD with the conventional dyssynchrony parameters SLD, MD and TsSD to discriminate between normal controls and CRT responders. XCD performed better than conventional parameters in discriminating responders from normal controls. XCD was also the only one that showed a decrease after CRT in responders. However, it is important to note that the temporal delay derived from the cross-correlation analysis may be inaccurate when the correlation is weak (e.g., correlation coefficient < 0.5). This concern may become important when using cross-correlation analysis to distinguish between CRT responders and non-responders.

In a recent study, Olsen et al showed that XCD was unable to distinguish between non-responders and responders. They used acceleration data instead of velocity data for cross-correlation analysis. Myocardial acceleration was computed from the differentiation of velocity data and was tentatively more close to contractility than velocity. The investigators evaluated the ability of cross-correlation analysis of systolic myocardial acceleration (XCA) with SLD and TsSD to discriminate between control groups (with narrow QRS) and CRT responders and between responders and non-responders. Similar to XCD, XCA discriminated CRT responders from control groups with a significantly higher area under curve (AUC) than SLD and TsSD (0.95 vs. 0.59 and 0.75, respectively). XCA also discriminated responders from non-responders (AUC = 0.66) but not significantly better than SLD (AUC = 0.55) and TsSD (AUC = 0.58).

With XCA, dyssynchrony in control subjects was found to be rare, whereas with conventional measures, dyssynchrony was found in > 30 % of control subjects. This finding suggests that conventional dyssynchrony metrics are less specific and overestimate the prevalence of mechanical dyssynchrony. Better specificity at detecting mechanical dyssynchrony by XCD or XCA may be useful for expanding the benefits of CRT to potential subjects who do not fulfill the current CRT criteria.

**Fourier analysis for strain uniformity**

Mechanical dyssynchrony can be quantified by the Fourier decomposition of myocardial strain. The Fourier analysis of each component of the strain is determined over time and space. The zero-order component $S_0$ of the Fourier decomposition is constant and represents perfectly synchronous contraction, whereas the first-order component, $S_1$, is sinusoidal and represents completely asynchronous contraction. The temporal uniformity of strain (TUS) or circumferential uniformity ratio estimate (CURE) index is calculated as the ratio of the sum of the synchronous segments ($S_0$) and the sum of the both $S_1$ and $S_0$ over time. For a perfectly synchronous motion, TUS or CURE index provides a value of 1, whereas for a completely asynchronous motion, it is equal to 0 (Figure 2).

Byrne et al. used the magnetic resonance imaging and CURE index to compare mechanical dyssynchrony and the impact of CRT on dyssynchrony between failing hearts with a right bundle branch block versus left bundle branch block. They found that mechanical dyssynchrony was less in right bundle branch block and CRT had less effect on failing hearts with right bundle branch block than those with left bundle branch block. Bertola et al. calculated the TUS index from speckle-tracking strain data. They found that radial TUS predicted response to CRT (AUC = 0.65), whereas dyssynchrony measure (TsSD strain) did not (AUC = 0.54) and was the only one that predicted LV ejection fraction improvement after CRT.

Fourier analysis of strain uniformity is a more sophisticated quantitative method as compared to conventional dyssynchrony assessment. The TUS (or CURE) index takes a geographic dispersion of strain into account and may differentiate temporal delays in contraction due to heterogeneity of a failing heart from temporal delays due to asynchronous activation. However, the analysis assumes a sine wave spatial variation in strain which may be not true in some patients. In addition, TUS are not very reproducible. From the Bland-Altman plots shown in the study of Bertola et al., the 95% limits of agreement are almost the same as the mean values of TUS.
New Approaches to Evaluate Dyssynchrony

**Figure 1.** Myocardial velocity traces and cross-correlation analysis of myocardial velocity. Arrows mark peak systolic velocities in velocity traces and temporal delay (TD) as well as maximum cross-correlation coefficients (XCC) in cross-correlation analysis plots. (A) Despite a large difference in time-to-peak systolic velocity (151 ms) in a normal subject, cross-correlation analysis reveals a high degree of synchrony: TD = 9 ms and XCC = 0.88. (B) Baseline date of a CRT responder. Velocity analysis shows significantly delayed peak of the posterior wall (98 ms). Cross-correlation analysis reveals a significant delay (TD = 162 ms). (C) Six-month follow-up data of a CRT responder. Velocity analysis shows a delayed peak of the posterior wall (63 ms) but cross-correlation analysis indicates a high degree of synchrony: TD = 0 ms and XCC = 0.9. AVO, aortic valve opening; AVC, aortic valve closure.
Analysis of mechanical discoordination

The poor performance of mechanical dyssynchrony metrics in the multi-center studies may be that time differences in onset or peak velocity or strain only partially reveal the mechanical disturbance of left ventricle in patients with a wide QRS duration. A more comprehensive assessment of regional myocardial mechanics may be achieved from indices describing mechanical discoordination, i.e. the amount and distribution of lengthening/shortening or thinning/thickening within the LV.

Figure 2. Three-dimensional plot of radial strain in a normal subject (A) and a CRT responder before (B) and 6 months after CRT (C) arranged according to time and ventricular location (left panels); temporal uniformity of strain (TUS) in the same subject evaluated by means of Fourier analysis (right panels). (A) TUS was 0.998, suggesting synchronous thickening around the ventricle. (B) Baseline TUS was 0.652, suggesting dyssynchrony. (C) TUS improved from 0.652 to 0.959, indicating resynchronization after 6 months of CRT.
Kirm et al. developed a novel discoordination measure, called internal stretch fraction (ISF), to quantify the relative circumferential lengthening (internal stretch) versus circumferential shortening during the ejection phase by tagging magnetic resonance imaging. The amount of stretch (or shortening) was calculated as the product of the number of regions with stretch (or shortening) and their average amount of stretch (or shortening), integrated over the ejection phase (Figure 3). They compared the new index with dyssynchrony metrics and found that only ISF could differentiate responders from non-responders.

It will be highly valuable to quantify ISF by echocardiography that makes its application and post-CRT

**Figure 3.** Radial strain rate plots and discoordination analysis (ISF) in a normal subject (A) and a CRT responder before (B) and 6 months after CRT (C). Tracings of strain rate of 6 mid-ventricular segments are represented as gray lines. The time course of the average thickening [e_p(t)] and average thinning [e_n(t)] are represented as blue line and red line, respectively. The amount of myocardial thickening (e_p) and thinning (e_n) during the ejection phase are represented with the area below curve e_p(t) and above curve e_n(t), respectively. Internal stretch fraction (ISF) was calculated as \(\left(\frac{e_n}{e_p}\right) \times 100\%\). (A) ISF was 0, suggesting no discoordination. (B) Baseline ISF was 118%, suggesting marked discoordination. (C) ISF decreased from 118% to 10%, indicating recoordination after 6 months of CRT. AVO, aortic valve opening; AVC, aortic valve closure.
follow-up more practical and cheaper, and lessens the burden for patients with heart failure. From our initial experience, mechanical discoordination could be quantified using speckle-tracking echocardiography.\textsuperscript{37} We found less discoordination in normal subjects and most CRT non-responders. An acute reduction in discoordination (recoordination) rather than resynchronization predicted LV reverse remodeling after CRT.\textsuperscript{37}

ISF is conceptually related to internal flow fraction, which can be measured by conductance catheter or magnetic resonance imaging and has been shown to decrease significantly after CRT.\textsuperscript{38,39} When there are alternating regions of myocardial expansion and contraction, blood will be sequestered in the heart rather than ejected to the systemic circulation. The internal flow fraction or ISF measures the overall inefficiency of the heart by comparing the amount of effective contraction with the amount of internal energy wasting.\textsuperscript{36-39} The advantage of ISF over conventional metrics is that it takes into account regional dispersion of strain during the ejection period, rather than at a single time point in a strain signal. The limitation of ISF is its dependency on timing of aortic opening and closure. The timing must be collected at different times with potentially different heart rates and loading conditions from when the mid-ventricular images were acquired, so that the marking of ejection phase adds a source of potential error to the quantification of ISF.

In the above sections, we describe the commonly used conventional dyssynchrony parameters and three new approaches for assessing mechanical dyssynchrony. Advantages and disadvantages of each echocardiographic method for the quantification of mechanical dyssynchrony are summarized in Table 1. Although the presence of LV dyssynchrony appears to play an important role in determining the response to CRT, many factors are associated with the outcome of CRT-treated patients. Comprehensive assessments of mechanical dyssynchrony, myocardial scar burden, the site of latest mechanical activation, and venous anatomy pre-operatively may help to identify those who will not derive any benefit or be potentially worsened.\textsuperscript{40,41}

**CONCLUSION**

Whenever a novel method develops that will open a

### Table 1. Advantages and disadvantages of echocardiographic methods for the assessment of mechanical dyssynchrony

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<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>M-mode\textsuperscript{17,18}</td>
<td>No specific echocardiographic machine is needed</td>
<td>Difficult to determine the timing of peak inward motion if the wall is akinetic or has complex motion</td>
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<td></td>
<td>Easy to perform</td>
<td>A high degree of variability</td>
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<tr>
<td>Color-coded tissue Doppler velocity\textsuperscript{8-10,16,19}</td>
<td>High temporal resolution</td>
<td>Susceptible to translational motion or tethering effect</td>
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<td></td>
<td>Allows simultaneous comparison of multiple segments</td>
<td>A high degree of variability</td>
</tr>
<tr>
<td>Radial strain by speckle tracking\textsuperscript{12,14}</td>
<td>Less affected by translational motion and tethering effect</td>
<td>Require specific software</td>
</tr>
<tr>
<td></td>
<td>Less variability</td>
<td>Less temporal resolution</td>
</tr>
<tr>
<td>Cross-correlation analysis\textsuperscript{31,32}</td>
<td>Nearly automated analysis</td>
<td>The calculated time delay may be inaccurate if the velocity correlation is weak</td>
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<tr>
<td></td>
<td>Less variability</td>
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<td></td>
<td>Rare dyssynchrony detected in normal subjects</td>
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<tr>
<td>Fourier analysis of strain uniformity\textsuperscript{33,35}</td>
<td>Nearly automated analysis</td>
<td>Sophisticated method</td>
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<tr>
<td></td>
<td>Allows assessment of geographic strain dispersion</td>
<td>Based on the assumption of a sine wave variation in strain</td>
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<tr>
<td>Discoordination analysis\textsuperscript{36,37}</td>
<td>Nearly automated analysis</td>
<td>Requires identification of ejection phase</td>
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new window into the heart function and disclose things that we have not appreciated previously. Advances in analysis and better understanding of dyssynchrony and discoordination will help us find an accurate, reliable and practical parameter for selecting CRT patients in the future. Until then, patient selection must use the parameter previously validated in landmark clinical studies: the QRS duration.

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REFERENCES


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