The role of tissue Doppler and strain imaging in predicting response to CRT

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Echocardiography; Pacing therapy; Doppler ultrasound; Congestive heart failure

Aims Several echocardiographic methods have been proposed to assist in patient selection for cardiac resynchronization therapy (CRT). The prevailing hypothesis is that echocardiography may be superior to the electrocardiogram to qualify abnormalities in regional mechanical activation, because QRS widening is only a surrogate for ventricular dyssynchrony.

Methods and results This review will focus on tissue Doppler (TD) and strain imaging, including their advantages and disadvantages for patient selection for CRT. Colour-coded TD remains to be one of the most promising means to quantify dyssynchrony. Tissue Doppler velocity data have a more favourable signal-to-noise ratio compared with TD strain or strain rate imaging. However, velocity data are affected by Doppler angle of incidence and passive or tethering motion. A newer promising method is speckle-tracking echocardiography to calculate strain. An opposing wall delay in peak TD velocity >65 ms has been associated with clinical and ventricular response to CRT. The initial experience with speckle tracking used the short-axis view to calculate radial strain. An anterior-septal to posterior wall peak strain delay >130 ms has been associated with an ejection fraction response to CRT.

Conclusion Although no ideal echo-Doppler method has yet been discovered to select patients for CRT, technical refinements and advances in understanding of pathophysiology continue to favourably impact on potential clinical applications.

Introduction
Cardiac resynchronization therapy (CRT) is an important advance for heart failure patients with depressed left ventricular (LV) ejection fraction and prolonged electrical activation. Patients have benefited from CRT by experiencing improvements in exercise capacity, quality of life, ventricular function, and survival.1-3 It is widely believed that timing abnormalities of regional mechanical activation, known as LV dyssynchrony, are the underlying pathophysiology that is improved by CRT.4-7 Multisite LV pacing from septal and free wall sites co-ordinates contraction of the dysynchronous regions, resulting in acute haemodynamic improvements and later improvements in LV size and function, known as reverse remodelling.8-10 However, not all patients have a similar favourable response to CRT. A great deal of attention has been focused on identifying the subset of patients who have a widened QRS complex, but lack sufficient dyssynchrony to benefit from CRT. Echocardiography has played a prominent role because it is widely available in many clinical settings and has high temporal and special resolution to quantify the timing of the dysynchronous segments.11-20 This review will summarise the specific applications of tissue Doppler (TD) and strain imaging, to quantify dyssynchrony and propose their potential role in patients undergoing CRT.

Tissue Doppler imaging
The largest body of published data for imaging to assess LV dyssynchrony and predict response to CRT exists for TD.8,9,11-19,21-24 Although both pulsed-TD and colour-TD modes exist, the vast majority of published data and clinical experience has been with colour-coded TD.25 Accordingly, the comments in this review will focus exclusively on colour TD. A recent multi-centre study, known as PROSPECT (predictors of response to resynchronization therapy) has shown that there can be high variability and suboptimal yield of TD for assessing CRT.17,26 Although the ability of TD to predict response to CRT in PROSPECT was less than anticipated, this was an important study because it highlighted that these technical factors may impact directly on the predictive value of TD measures of dyssynchrony and that the successful use of TD requires a high level of expertise (Table 1). Accordingly, the current consensus is that no ideal echocardiographic method exists to confidently exclude patients from CRT, and that the routine patient selection criteria should be adhered to.7,20 Nonetheless,
TD and strain imaging to predict response to CRT

TD measures of dyssynchrony play an intriguing potential role in the care of the CRT patient, in particular if a simplified and highly reproducible method may be applied.

Several post-processing TD methods exist, including displacement imaging, strain rate, and TD strain imaging. Several authors have had differences of opinion on the preferred approach.

Tissue Doppler data are intimately affected by ultrasound beam angle of incidence, and velocity cannot differentiate active from passive motion. However, because the fundamental determination of the Doppler equation is velocity, it appears that TD velocity data have the best balance of a robust signal-to-noise ratio and relatively more simple analysis that can be applied to most patients. A key technical element appears to be the need for an ultrasound system with colour-TD capabilities at high frame rates >100 Hz. This is because the wide-sector scanning of colour-TD systems may result in lower frame rate image acquisition which can impact the temporal resolution to accurately characterize LV mechanical dyssynchrony. A second key element is a careful and systematic approach to the user interface for off-line analysis. Since the goal is to determine the timing of a particular LV segment, the user must employ a manual spatial averaging approach to derive the most reproducible TD velocity signal. This is accomplished by defining the myocardial area of interest for tissue velocity sampling, then using visual feedback from the TD velocity curves in order to manually fine-tune the sampling area to produce the strongest signal-to-noise ratio. This process requires a relatively large region of interest (ROI) for TD signal averaging over an area of the myocardium (7 × 15 mm, for example) with the operator then moving the ROI within the LV segment, searching for the most reproducible signal without high-frequency noise. This step appears to be one of the most important steps to determine a reproducible time–velocity curve.

Among the TD velocity approaches that have been advocated, the vast majority support limiting the analysis of peak velocity to the ejection period. This is to exclude the isovolumic contraction spike before ejection, and in particular, exclude the post-systolic high-velocity spikes occurring after aortic valve closure, which are non-specific. The post-systolic velocity data may be particularly misleading in patients with ischaemic heart disease and scar that has a large amount of post-systolic recoil that is a confounding variable to dyssynchrony analysis. The simplest approach is to determine aortic valve opening and aortic valve closure from the routine blood flow Doppler signal sampled from the LV outflow tract, with this timing transferred to the TD time–velocity analysis of the LV walls. The most straightforward method is to determine the opposing wall delay by measuring the difference in time to peak ejection velocities between septal and lateral wall segments in the apical four-chamber (Figures 1–3) or long-axis view. The most widely used cut-off value for significant dyssynchrony is an opposing wall delay of >65 ms. The apical two-chamber view may be an alternative, but the four-chamber and apical long-axis views that contain septal and free-wall segments within the same plane have the highest yield for detecting dyssynchrony. An alternate method is the 12-site standard deviation method, also known as the Yu index. The most reproducible segmental peak velocities are sought from basal and mid-ventricular levels of the LV walls in the apical four-chamber, two-chamber, and long-axis view to yield 12 segments. An identical method of manual signal averaging is followed, moving the ROI within the segment inferiorly–superiorly, and side-to-side within the wall to determine the optimal peak velocity during ejection that is most reproducible without signal noise. One then needs to measure the time from the onset of the QRS complex to 12 corresponding peak velocities, followed by calculating the standard deviation (SD) of those values. A cut-off value often used as significant dyssynchrony for the Yu index is an SD of ≥33 ms. The Yu index appears to be an accurate means to qualify LV dyssynchrony, but is more complex than the opposing wall delay method described above, and may be too difficult to apply in some clinical laboratories for routine clinical use.

Tissue Doppler strain imaging has, most frequently, been applied to the apical views to assess LV longitudinal shortening. For TD strain imaging to perform successfully, it requires LV wall deformation to be in the same direction as the Doppler angle of incidence. In other words, the longitudinal shortening of the LV segment must be oriented along the ultrasound scan line for reliable data acquisition. Unfortunately, this represents a limitation in many heart failure patients evaluated for CRT because of spherical geometry encountered, which affects Doppler data quality. It is theoretically advantageous to integrate velocity data to determine strain, and TD strain imaging may provide useful information. However, when applied to a large series of consecutive patients with heart failure and depressed ejection

<table>
<thead>
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<th>Method</th>
<th>Cut-off</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Colour tissue Doppler peak velocities</td>
<td>Opposing wall delay ≥65 ms</td>
<td>Robust signal strength. Wide experience and multiple supportive studies published</td>
<td>Experience and training required for data analysis. Requires specialized equipment. Cannot differentiate active from passive motion</td>
</tr>
<tr>
<td>Speckle-tracking radial strain</td>
<td>Anteroseptal-posterior wall delay ≥130 ms</td>
<td>Can be applied to routine grey-scale images. Differentiates active from passive motion</td>
<td>Experience and training required for data analysis. Requires specialized equipment. Limited clinical experience from many centres</td>
</tr>
<tr>
<td>Interventricular mechanical delay</td>
<td>Right ventricular to left ventricular ejection delay ≥40 ms</td>
<td>High yield and high reproducibility. No special equipment required. Simple analysis</td>
<td>Appears to lack sensitivity and specificity of intraventricular dyssynchrony approaches</td>
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Figure 1  An example of colour-coded tissue Doppler image using the apical four-chamber view from a normal volunteer demonstrating synchronous peak velocities in the septal and lateral wall (arrow), determined between aortic valve opening (AVO) and aortic valve closure (AVC).

Figure 2  An example of colour-coded tissue Doppler image using the apical four-chamber view from a patient with heart failure and significant mechanical dyssynchrony before cardiac resynchronization therapy. The opposing wall delay in peak velocities (arrows) from septal to lateral wall is 120 ms. Peak velocities are determined between aortic valve opening (AVO) and aortic valve closure (AVC). This patient had a favourable clinical and ventricular function response to resynchronization therapy.
fraction, it frequently had too much signal noise, which affected data quality.\textsuperscript{19,27,28} Undesirable signal noise was even more prominent when using TD strain rate imaging in patients evaluated for CRT. TD strain imaging has also been applied to short-axis images, to assess anteroseptal to posterior wall delay. In a study by Dohi et al.,\textsuperscript{31,32} TD radial strain was predictive of acute hemodynamic response to CRT. However, in comparison to radial strain assessed by speckle tracking, discussed subsequently, TD radial strain imaging is more technically demanding and affected by signal noise. Further refinements in TD strain imaging continue to emerge, but at the present time, TD velocities appear to have an advantage to TD strain imaging from the longitudinal plane to assess LV dyssynchrony.

Speckle-tracking strain imaging

Speckle tracking is a relatively new advance that may be applied to routine grey-scale echocardiographic images. The speckle-tracking software tracks patterns of speckle within the myocardial wall to determine relative thickening and thinning, or shortening and lengthening. The initial experience for CRT was using the short-axis images to calculate radial strain, or $\%$ wall thickening.\textsuperscript{33} This has several advantages, including the ability to differentiate active thickening from passive motion and to focus on short-axis dynamics, which appear to be more prominent in LV dyssynchrony than longitudinal dynamics.\textsuperscript{34} The first step is to acquire a high-quality short-axis view of the left ventricle, usually at the mid-LV level. Care must be taken to ensure that the short-axis image be oriented as circular as possible, to detect wall thickening towards the LV cavity centre, as a point of reference. Oblique image planes may yield erroneous data. Frame rates are also important, with an optimal range of 60–80 Hz. Frame rates $<30$ Hz are too slow to yield adequate temporal resolution, and frame rates $>100$ Hz result in difficulties for the speckle-tracking algorithm to track adequately. The next important step is to apply the ROI carefully. ROI placement has an important impact on the data quality. A single beat is usually analysed, and the gating of the electrocardiogram should be set to begin with the very onset of the QRS complex in order to include very early systolic events. The inner endocardial ROI should be drawn slightly within the LV cavity. This is important to accurately capture septal thickening. The outer ROI should be adjusted to encompass the LV epicardium. This wide ROI appears to result in the most reproducible time–strain curves. The next step is to inspect the time–strain curves so that they do not contain excessive signal noise. The ROI should be re-drawn if tracking quality is poor, or if time–strain curves are viewed to be inadequate. Our experience is that the anteroseptal and posterior wall segments usually yield the most reproducible data. The reason for this in not known with certainty, but these regions are most perpendicular to the ultrasound beam and may produce the highest quality tissue ultrasonic signal for speckle tracking to follow. Accordingly, the timing of the anteroseptal to posterior wall segments appears to have the highest yield for predicting response to CRT, with a cut-off of $\geq 130$ ms (Figures 4–6). It should be noted that end-systolic strain or peak positive $\%$ thickening occurs much later in the cardiac cycle than the peak

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure3.png}
\caption{An example of colour-coded tissue Doppler image using the apical four-chamber view from a heart failure patient with widened QRS, but no significant mechanical dyssynchrony before cardiac resynchronization therapy. There was similar timing in peak velocities (arrows) from septal to lateral wall, determined between aortic valve opening (AVO) and aortic valve closure (AVC). This patient did not have a favourable clinical nor ventricular function response to resynchronization therapy.}
\end{figure}
Figure 4  An example of speckle-tracking radial strain using the mid-ventricular short-axis view from a normal volunteer demonstrating synchronous peak radial strain curves (arrow).

Figure 5  An example of speckle-tracking radial strain using the mid-ventricular short-axis view from a patient with heart failure and significant mechanical dyssynchrony before cardiac resynchronization therapy. The anteroseptal to posterior wall delay was 322 ms. This patient had a favourable clinical and ventricular function response to resynchronization therapy.
velocity events. This explains why the cut-off value for strain is much greater than the TD velocity cut-off. A large two-centre study has shown that the TD velocity data and speckle-tracking radial strain have combined predictive value. If both longitudinal dyssynchrony by TD velocity and radial dyssynchrony by speckle-tracking strain are present, patients have a high likelihood of an ejection fraction response to CRT. Conversely, if neither longitudinal dyssynchrony by TD velocity nor radial dyssynchrony by speckle-tracking strain is present, patients have a low likelihood of an ejection fraction response to CRT. Patients with heterogeneous patterns of dyssynchrony with either longitudinal or radial dyssynchrony present, but not both, have an intermediate ejection fraction response. Most of these patients with heterogeneous dyssynchrony patterns were observed to have ischaemic heart disease and some degree of scar. Patients with ischaemic heart disease in this study, as in others, were found to have a lower ventricular functional response rate than patients with non-ischaemic forms of heart failure. Accordingly, it is not clear whether the heterogeneous pattern is simply associated with ischaemic heart disease or has an alternate explanation yet to be elucidated.

Alternate echo-Doppler means to assess dyssynchrony

Another important lesson learned form the PROSPECT study is that the routine pulsed-Doppler measures of interventricular mechanical delay (IVMD) have a high yield and are very reproducible. IVMD is measured from data using pulsed Doppler with a sample volume placed proximal to the pulmonic valve (basal short-axis view) and then placed proximal to the aortic valve (apical five-chamber or long-axis view). The time interval from the onset of the QRS complex to the onset of pulmonic flow is subtracted from the time interval from the onset of the QRS complex to the onset of aortic flow to yield IVMD. The most widely used cut-off of ≥40 ms has been shown to indicate significant interventricular dyssynchrony that is responsive to CRT. An even longer IVMD of ≥49 ms was shown to be associated with patient outcome in the CARE-HF study. A severe IMVD appears to be a marker for severe dyssynchrony. An explanation for the relationship of IMVD to intraventricular LV dyssynchrony that is measured by TD or strain imaging may be that significant intraventricular dyssynchrony delays LV ejection, which is detected by IVMD. Although this precise relationship has yet to be elucidated, it is reasonable to assess IVMD as a additional simple measure to the overall dyssynchrony analysis in patients being evaluated for CRT.

Current and future applications

Current applications of all echo-Doppler methods to assess LV dyssynchrony in patients evaluated for CRT are controversial. In the wide QRS complex patients, currently defined as >120 ms, routine implantation criteria are advocated including heart failure functional class III or IV (on optimal medical therapy) and depressed ejection fraction ≤35%. The consensus is that patients who meet these criteria should have CRT, and that an imaging dyssynchrony study
should not be part of their selection. The next frontier is to use these echo-Doppler methods to identify patients with narrow QRS complexes and mechanical dyssynchrony who may potentially benefit from CRT.\(^4,40\) The Rethinq study was the first randomized CRT study in patients with QRS complex < 130 ms.\(^41,42\) Patients were randomized if they had significant LV dyssynchrony, defined by M-mode or a TD velocity opposing wall delay ≥ 65 ms. It was a relatively small study with mixed results that may have been underpowered to be conclusive. CRT had no effect on the primary endpoint of peak oxygen consumption, but had a significant favourable effect on New York Heart Association Functional Class, which was a secondary endpoint. The Rethinq results were not entirely discouraging because perhaps better patient selection or better dyssynchrony criteria may result in a convincing therapeutic benefit of CRT in these patients. Interestingly, patients with QRS duration in the range of 120–130 ms with echo-Doppler evidence of dysynchrony showed significant benefit when randomized to CRT.\(^43\) Accordingly, it appears that there may be a role for echo-Doppler dyssynchrony information in patients with borderline QRS complex durations ~120 ms, currently. Evaluation of the patient for dyssynchrony with a borderline QRS duration, or perhaps the borderline ejection fraction or borderline heart failure functional class, is reasonable in selected clinical scenarios. Of the many techniques proposed, TD longitudinal velocities, speckle-tracking radial strain, and IVMD currently appear to be among the most promising. Undoubtedly, refinements in the technology of the ultrasound equipment and our understanding of the role that dyssynchrony along with other confounding variables play in the CRT patient will result in an evolution of the approach. This remains a fascinating field with great promise to improve the therapeutic applications of CRT to benefit our patients with heart failure.

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