Clinical utility of speckle-tracking echocardiography in cardiac resynchronisation therapy

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Abstract
Cardiac resynchronisation therapy (CRT) can profoundly improve outcome in selected patients with heart failure; however, response is difficult to predict and can be absent in up to one in three patients. There has been a substantial amount of interest in the echocardiographic assessment of left ventricular dyssynchrony, with the ultimate aim of reliably identifying patients who will respond to CRT. The measurement of myocardial deformation (strain) has conventionally been assessed using tissue Doppler imaging (TDI), which is limited by its angle dependence and ability to measure in a single plane. Two-dimensional speckle-tracking echocardiography is a technique that provides measurements of strain in three planes, by tracking patterns of ultrasound interference ('speckles') in the myocardial wall throughout the cardiac cycle. Since its initial use over 15 years ago, it has emerged as a tool that provides more robust, reproducible and sensitive markers of dyssynchrony than TDI. This article reviews the use of two-dimensional and three-dimensional speckle-tracking echocardiography in the assessment of dyssynchrony, including the identification of echocardiographic parameters that may hold predictive potential for the response to CRT. It also reviews the application of these techniques in guiding optimal LV lead placement pre-implant, with promising results in clinical improvement post-CRT.

Introduction
Heart failure can be defined as the inability of the heart to deliver oxygen to meet the metabolic requirements of the body, due to an abnormality in the cardiac structure or function (1). The characterisation of cardiac dyssynchrony has led to a better understanding of the mechanisms that underlie the compromise in cardiac stroke volume in some forms of heart failure. CRT aims to achieve inter- and intra-ventricular synchrony by pacing the right ventricle (RV) and left ventricle (LV) simultaneously, with pacing leads positioned in the right ventricle and coronary sinus, respectively. In patients with sinus rhythm, CRT also aims to restore atrioventricular (AV) synchrony. It has made a substantial improvement in the clinical outcomes (including hospitalisation and mortality) in appropriately selected patients with heart failure (2) and is recommended in cases of drug-refractory New York Heart Association class II–IV symptomatic heart failure, an ejection fraction <35% and ECG evidence of left bundle branch block (LBBB) (3). However, up to one in three patients do not show an improvement post-CRT (4, 5).
Numerous echocardiographic indices of dyssynchrony have been evaluated, based on M-mode, pulsed Doppler and tissue Doppler (TDI) methods (6). However, they have yielded mixed results in their ability to predict CRT response, with observational studies demonstrating a link between the presence of dyssynchrony and an improvement post-CRT; however, larger trials show poor technique agreement and reproducibility (7, 8). Over the last 15 years, speckle-tracking echocardiography (STE) has emerged as a method for assessing global and regional LV systolic function through the measurement of myocardial deformation and has been applied to the evaluation of dyssynchrony in potential candidates for CRT. This article describes the technique of STE and reviews its role in guiding patient selection for CRT.

**Mechanisms of dyssynchrony**

Cardiac dyssynchrony comprises three main components: atrioventricular (AV), inter-ventricular and intra-ventricular. AV dyssynchrony describes a delay in the normal sequential atrioventricular contraction, resulting from delayed conduction through the AV node. This leads to disordered ventricular diastolic filling and ultimately to a reduced LV preload that compromises stroke volume (due to loss of the Starling mechanism) (9). The mechanisms involved include (i) initiation of ventricular systole while the ventricular is still filling, resulting in mitral regurgitation; (ii) shortened ventricular filling time and (iii) the occurrence of atrial systole simultaneously with early passive filling (10). Inter- and intra-ventricular dyssynchrony have a relatively greater effect on ventricular pump function than AV dyssynchrony (9). Inter-ventricular dyssynchrony describes a sequential delay in activation between the RV and LV, resulting in a lack of co-ordinated contraction. In LBBB, the anterior surface of the RV is the earliest to depolarise (due to fast electrical propagation through the intact right bundle), and the posterolateral basal LV is usually the latest (due to the relatively slow propagation from cell to cell) (11). Intra-ventricular dyssynchrony can result from the temporal delay in electrical activation of one region of the LV myocardium relative to another, such as that observed in LBBB. However, it can also exist in the absence of regionally delayed electrical activation, where abnormal myocardial loading is considered instead of contributing to dyssynchrony (11).

Intra-ventricular dyssynchrony leads to LV contraction that is inferior in both effectiveness and energy efficiency. In early systole, the septum contracts, whereas the lateral wall that faces it is passively stretched. The reverse of this pattern is seen in late systole, when lateral wall contraction results in septal stretching. The late-activated septal wall contracts forcefully (due to earlier stretch), but against a high LV cavity pressure. The successive contraction and stretching wastes myocardial energy and compromises efficiency. The haemodynamic consequences of dyssynchronous LV contraction are reduced stroke volume, stroke work and slower rate of rise of LV pressure and increased LV end-systolic wall stress. In addition, the LV end-systolic pressure–volume relationship shifts to the right, denoting that the LV now operates at a larger volume in order to recruit the Frank–Starling mechanism (9, 11).

By restoring AV, inter- and intra-ventricular synchrony, CRT is able to produce acute and sustained improvements in LV contractility, and response can be gauged by the improvement in LV contractility. This is measurable acutely as an increase in dP/dT and arterial pulse pressure, and a decrease in pulmonary capillary wedge pressure (12).

**Echocardiographic assessment of LV dyssynchrony**

Various techniques have been explored to assess the presence of LV dyssynchrony. M-mode can be used to measure the time delay between contraction of the LV anteroseptal and posterior walls. Although this is relatively quick to perform, it is assumed that these two LV walls reflect the presence or absence of dyssynchrony within the entire ventricle. Its ability to predict echocardiographic and clinical outcome post-CRT (13) has not been reproducible between different groups (14).

TDI allows a greater number of LV segments to be sampled compared with M-mode. Pulsed Doppler method is used to sample the longitudinal shortening velocity profile of up to six basal LV segments from the apical views (15). By measuring the time delay between the onset of the QRS and the peak systolic velocity, electromechanical delay can be quantified. The dyssynchrony index is then expressed as the dispersion of regional electromechanical delays. This has been shown by various groups to predict the improvement in exercise capacity, symptoms and echocardiographic parameters including LV volumes and ejection fraction (16, 17, 18). Extending the sampling from the six basal LV segments to the six mid-LV segments provides the standard deviation of electromechanical
delay (Ts-SD) in the 12 non-apical LV segments. This may be a more accurate predictor of CRT response than other TDI techniques (19). The limitations of TDI include the need for a high imaging frame rate and several separate acquisitions. Furthermore, as with any Doppler technique, the ultrasound beam must be aligned as parallel as possible to the sampling region of interest.

Real-time 3D echocardiography provides a dataset containing the entire LV. This can then be divided into 16 or 17 sub-volumes (corresponding to the standard myocardial segments) to derive time–volume curves for each segment. The standard deviation of the time to peak segmental contraction can be reproducibly quantified in patients with LV dysfunction and is an independent predictor of CRT response (20).

It is possible that conventional TDI measurements may also detect dyssynchrony in the presence of heterogeneous intra-ventricular activation sequences, which are not necessarily correctable by CRT. More novel approaches to the assessment of dyssynchrony have included focus on electromechanical (as opposed to mechanical) abnormalities. An example of this is ‘septal flash’: the abnormal brief inward septal motion that occurs during the isovolumic contraction time and which characterises LBBB-related dyssynchrony. An observational study of over 1000 patients (PREDICT-CRT) demonstrated that the presence of apical rocking and septal flash had an incremental value over clinical variables and QRS width for identifying CRT responders (21). In addition, their absence or unsuccessful correction was associated with a high risk for non-response and unfavourable long-term survival.

Using an approach that considers all three components of dyssynchrony and also incorporates the presence of a correctable mechanical abnormality is predictive of response to CRT and survival. Using pre-defined mechanical abnormalities such as septal flash, abnormalities in LV filling and prolonged inter-ventricular delay, Doltra and co-workers demonstrated that some abnormalities correlated more strongly with CRT response than others and that the absence of any mechanical abnormality greatly increased the likelihood of CRT non-response (22).

### Measuring myocardial deformation using TDI and STE

TDI was one of the earliest techniques developed to measure myocardial deformation, or ‘strain’. By measuring LV longitudinal shortening velocities over time, the velocity gradient between two points in the myocardial wall can be used to calculate strain rate. This is then used to derive strain. As it is a Doppler-based method, TDI is only able to assess deformation in the plane incident with the ultrasound beam and requires acquisition of dedicated images (23).

More recently, myocardial deformation imaging has been performed through the use of speckle-tracking echocardiography (24). This uses the presence of natural acoustic markers in B mode grey-scale images that are created by interference of ultrasound beams within myocardial tissue and are denoted as ‘speckles’ (25). They are equally distributed throughout the myocardium, and tracking their relative positions through each frame of the cardiac cycle provides information on regional myocardial deformation, known as ‘strain’. Strain reflects the percentage change of the myocardial length from its original value, with thickening represented by a positive strain value and shortening represented by a negative strain value. During systole, the LV shortens in the longitudinal and circumferential planes and thickens in the radial plane.

Radial and circumferential strains are obtained from LV short-axis images at the level of the mitral valve, papillary muscles and apex. Longitudinal strain is obtained from apical 4-, 3- and 2-chamber images. In contrast to TDI, the analysis is performed offline and requires semi-automated positioning of the endocardial contour, following which the software tracks the speckles through the cardiac cycle. Operator adjustment of the tracking is possible by manual correction of the contour. The myocardium is divided into segments in each view, so the final display of strain in each plane takes the form of segmental time–strain curves. The analysis of longitudinal and radial strain is shown in Fig. 1. The advantages of STE over TDI for the determination of strain include relatively less angle dependence in the sampled area, as the speckles are tracked along the direction of movement of the myocardial wall, instead of the direction of the ultrasound beam (23, 26). However, it should be noted that STE is not entirely independent of angle, as axial versus lateral resolution remain critical for this method too. In addition, lower inter-observer variability and less time-consuming analysis have been demonstrated for STE-derived strain compared with TDI-derived strain (27).

Compared with TDI, which reflects myocardial motion, but also translational movement of the heart within the thoracic cavity, strain reflects shortening of the myocardium, irrespective of the movement of the whole
heart (28). Disadvantages include the requirement of STE for high-resolution image quality and the potential for different tracking algorithms to produce different results (23), although this inter-vendor variation has been largely eliminated on the latest ultrasound systems.

The assessment of myocardial dyssynchrony using STE includes measuring the maximum time delay between peak systolic strain of two segments (usually between the anteroseptal and posterolateral walls) and the dyssynchrony index of the LV (taken from the standard deviation of time to peaksystolic strain, Fig. 2). In practice, speckle tracking in the short-axis images is more reliable than in the apical images, as non-valid tracking of apical segments can present a problem. However, studies have shown that longitudinal strain is more reproducible than circumferential and radial strains (29, 30), as short-axis views are more sensitive to out-of-plane motion of the speckles.

Measurements of strain and strain rate show good agreement between TDI and 2D STE (31, 32). It should be noted that a combined approach of TDI and speckle tracking to obtain longitudinal velocity and radial strain, respectively, has been shown to increase the predictive value of response to CRT compared with either technique alone (33).

### Evidence for 2DSTE in predicting response to CRT

CRT involves simultaneous pacing of the RV and the posterolateral wall of the LV. Although it has made a significant impact on clinical outcomes in heart failure (2), the incidence of non-responders remains a problematic issue and has been estimated as approximately one in three patients (4, 5). In the literature, at least 17 different criteria have been suggested for defining a good response to CRT, eight of which are echocardiographic (including but not limited to): an increase in ejection fraction >5% to >15%, a decrease in LV end-systolic volume >10% to >15%, a decrease in LV end-diastolic volume >15% and an increase in stroke volume >15% (34). There is no current consensus on agreed criteria, although many recent studies have used the decrease in LV end-systolic volume >15% to define response (28, 35).

Although the electrocardiogram (ECG) has provided robust predictors of CRT response in the form of QRS width and the presence of left bundle branch block (LBBB), it is less sensitive than echocardiography in detecting lesser degrees of mechanical dyssynchrony. Over the last 15 years, various studies have sought to...
identify echocardiographic markers of dyssynchrony that can reliably predict the response to CRT. The multi-centre PROSPECT trial studied 12 echocardiographic parameters of dyssynchrony and found that although several parameters differed between CRT responders and non-responders, they showed only modest sensitivity and specificity. The investigators concluded that no single parameter could reliably improve patient selection for CRT (8). However, there was a wide variability in the analysis of echocardiographic measures, and a sub-analysis identified the pre-ejection interval, inter-ventricular mechanical delay and TDI longitudinal velocity as predictors of the LV end-systolic volume response and improvement in CCS (36).

Subsequent studies with longer follow-up periods (3–4 years) have identified speckle-tracking radial strain dyssynchrony (discussed above) as a predictor of clinical benefit in patients with ischaemic cardiomyopathy undergoing CRT (37, 38, 39). It is associated with outcome independently of the QRS width (38) and is an independent predictor of long-term survival (37). Using a value of ≥130 ms, STE radial dyssynchrony predicts the ejection fraction response 8 months post-CRT with 89% sensitivity and 83% specificity (28). Furthermore, the absence of radial strain dyssynchrony is associated with a poorer outcome in patients with a QRS width of <150 ms (38, 39).

The prospective multi-centre Speckle Tracking and Resynchronisation (STAR) study demonstrated that among the different types of strain, radial strain had the highest sensitivity for predicting ejection fraction response in patients undergoing CRT (sensitivity 86% and specificity 67%) (39). Circumferential and longitudinal strains predicted response when dyssynchrony was detected, but failed to identify dyssynchrony in one-third of patients who responded to CRT. Another group also found that radial strain dyssynchrony correlated better with long-term effects post-CRT than circumferential and longitudinal strain-based dyssynchrony (35).

The above studies enrolled patients with a mean QRS duration of 150–167 ms. However, the benefit of CRT appears to be relatively smaller in patients with a QRS width <150 ms (4, 40), and this is reflected in the ESC guidelines, in which LBBB with a QRS duration of 120–150 ms is a class IB rather than IA indication for CRT (3). However, the complementary assessment of mechanical dyssynchrony by echocardiography can improve selection even in this patient group. This again relates to the concept that the surface ECG will not necessarily detect abnormalities of regional mechanical activation that result in mechanical dyssynchrony. Supportive of this theory are the results of the CARE-HF trial, in which patients with a QRS duration of 120–149 ms experienced better survival and fewer cardiac hospitalisations when the following echocardiographic
criteria for dyssynchrony were used to guide CRT implantation: aortic pre-ejection delay >140 ms, inter-ventricular mechanical delay >40 ms and delayed activation of the posterolateral LV wall (41). However, benefits are questionable when the QRS width is <130 ms, and the large, multi-centre, randomised Echo CRT trial was stopped early due to an apparent increase in mortality in the CRT-on group (42).

Speckle-tracking radial strain dyssynchrony has also been used to characterise dyssynchrony in CRT-D patients with severe symptomatic heart failure (43). The persistence of, or development of, radial strain dyssynchrony was strongly associated with the rate of ventricular arrhythmia and combined end point of arrhythmia, death, transplantation or LVAD implantation.

Longitudinal strain dyssynchrony is also an independent predictor of response to CRT (44, 45). Longitudinal strain is able to distinguish ischaemic from non-ischaemic LBBB (46). On bull’s eye mapping, the peak systolic strain shows a basal septal ‘horseshoe’ pattern of reduced regional strain in patients with non-ischaemic LBBB. This is of particular importance in assessing the suitability for CRT, as patients with non-ischaemic cardiomyopathy are better responders than those with ischaemic cardiomyopathy (3).

Randomised control trials have clearly demonstrated that LBBB morphology is a strong predictor of CRT response. Indeed, LBBB-induced dyssynchrony is characterised by septal flash, which strongly correlates with response to CRT (47). Recent work has demonstrated that the identification of this septal flash by longitudinal strain (LBBB longitudinal pattern) is associated with CRT response and long-term outcome (48). Three patterns of LV septal deformation have been identified (Fig. 3): double-peaked systolic (pattern 1), early pre-ejection peak followed by prominent systolic stretch (relaxation and lengthening of the myocardium; pattern 2) and pseudonormal shortening with late-systolic peak and smaller end-systolic stretch (pattern 3). Patterns 1 and 2 are associated with better improvements in echocardiographic outcomes and event-free survival post-CRT compared with pattern 3 (49).

In addition, the time delay in radial strain corresponds to the delay between the septal flash and the posterior wall. The septal-to-posterior wall motion delay is bimodal owing to the septal flash (50). Combining the strain dyssynchrony index derived from radial, circumferential and longitudinal strains holds better predictive value for CRT outcome than using a single parameter alone (51).

RV dyssynchrony parameters add incremental value to LV dyssynchrony parameters in the evaluation of candidates for CRT (52). The use of STE to assess RV dysfunction (using global longitudinal strain) has demonstrated that RV dysfunction is associated with poor short-term and long-term prognosis after CRT implantation (53). Preserved RV function is an independent predictor of long-term event-free survival after CRT (54).

The role of 2DSTE in guiding CRT lead placement

Myocardial tissue Doppler method has been used to identify the site of latest mechanical activation in the LV of patients with heart failure. When this information is used to guide the optimal position of the ‘LV’ lead during CRT, it substantially improves clinical and echocardiographic outcomes compared with discordant lead placement (55). Speckle-tracking echocardiography has built on this potential, and when radial strain data are used for guiding lead placement, improvements have been observed in LV ejection fraction (28), LV reverse remodelling, all-cause mortality and heart failure hospitalisations, compared with discordant lead placement (37, 56). These results have also been borne out in large, randomised clinical trials. The TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronisation Therapy) trial (57) used speckle-tracking radial strain to guide LV lead positioning and also to identify sites of scar, with beneficial effects on LV reverse remodelling and clinical outcomes at 6 months. The STARTER (Speckle Tracking Assisted Resynchronisation Therapy for Electrode Region) trial (58) determined the latest time to peak strain in the LV basal and mid-wall short-axis segments and found a reduction in the combined end point of death and heart failure hospitalisation.

Although cardiac magnetic resonance (CMR) remains the gold standard for quantifying myocardial scar, speckle-tracking strain can also serve as a useful adjunct in patients in whom CMR is contraindicated. The ideal cut-off value for radial strain is yet to be determined, with values of <16.5% (37) and <10% (57, 59) having been used to denote scar, and holding predictive value for LV reverse remodelling and clinical outcomes.

3D speckle-tracking echocardiography

The limitations of 2D speckle-tracking echocardiography pertain to its ability to track speckles obtained from 2D
images, whereas cardiac motion comprises rotation, contraction and shortening in three dimensions. Thus, some speckles may be lost in through-plane motion during the cardiac cycle (25). This applies particularly to longitudinal displacement in apical views and to radial and circumferential displacement in short-axis views. Loss in through-plane motion is more frequently found in radial and circumferential strains than in longitudinal strain.

3D speckle-tracking echocardiography allows acquisition of 3D indices of the entire LV from a 3D dataset acquired in the full-volume mode with an apical view (60). In the apical plane, three reference points are set by the user: two at the base of the LV at the mitral valve level and one at the apex. The same three points are fixed on a second orthogonal plane. The epicardial border can be entered manually or by setting a default ‘thickness’ for the myocardium. After detection of the myocardial borders at the end-diastolic reference frame, the user can correct the shape of the LV reference at the starting image. The 3D images of the LV wall are automatically divided

Figure 3
(A) Characterisation of LV septal deformation patterns using speckle-tracking longitudinal strain. Double-peaked systolic shortening (A, pattern 1), early pre-ejection shortening peak followed by prominent systolic stretch/lengthening (B, pattern 2) and pseudonormal shortening with a late-systolic shortening peak and less pronounced end-systolic stretch (C, pattern 3). Patterns 1 and 2 are associated with better improvement in echocardiographic outcomes and event-free survival post-CRT compared with pattern 3. (D) Example of a patient with severe heart failure, LBBB (QRS width 180 ms) and septal deformation pattern 2. Response to CRT with reduction in LV volumes and improvements in LV function and GLS is demonstrated. Reprinted from Journal of the American Society of Echocardiography, Vol 27, Marechaux S, Guiot A, Castel AL, Guyomar Y, Semichon M, Delelis F, Heuls S, Ennezat PV, Graux P & Tribouilloy C, Relationship between two-dimensional speckle-tracking septal strain and response to cardiac resynchronization therapy in patients with left ventricular dysfunction and left bundle branch block: a prospective pilot study, pp 501–511, Copyright (2014) American Society of Echocardiography, with permission from Elsevier.
into 16 segments. The software automatically tracks the contour on the subsequent frames in the three different strain vectors simultaneously. The feasibility of acquiring 3D volumes is approximately 70% (61).

Discordant values for strain have been demonstrated when comparing data obtained from 3D vs 2D techniques, with circumferential strain being reportedly greater and longitudinal strain being smaller with 3D speckle-tracking echocardiography (62). This has been attributed to the full appreciation of 3D cardiac motion by 3D tracking, which is not possible in the cross-sectional image plane of 2D tracking techniques. However, there appears to be a close correlation between 2D and 3D dyssynchrony indices (63). An advantage of the 3D tracking technique is the potential for faster analysis of strain compared with the 2D tracking method, as all the three strain vectors are analysed simultaneously, as opposed to sequentially (62, 64). It can also assess a greater proportion of myocardial segments compared with 2D tracking, independent of the quality of the patient’s acoustic window. A disadvantage of 3D STE is relatively low temporal resolution (65) and a high dependence on image quality. Thus, when the acoustic window is poor, dropout in the endocardial border can result in inappropriate tracking and inaccurate strain curves.

3D STE can be used to quantify the LV dyssynchrony in patients referred for CRT (63) and has identified the site of latest mechanical activation as mid and basal posterior walls in most cases, followed by mid and basal lateral walls. This agrees with the data obtained from 2D STE (56). A U-shaped propagation of LV activation is associated with LBBB and with a favourable response to CRT (66).

Controversies

Various echocardiographic methods now exist for the potential evaluation of dyssynchrony, along with a multitude of apparently robust predictors of CRT response. However, a number of challenges exist in the acquisition and interpretation of data required for dyssynchrony analysis. For example, the TDI signal shows significant sensitivity to the position of the sampling region. It can be challenging to differentiate physiological signal versus noise. Perhaps it is not surprising that considerable intra-observer and inter-observer variability exists, even in the clinical trial setting.

STE is also subject to errors in interpretation, due to loss of through-plane motion, and the potential for different tracking algorithms to produce different results. STE for CRT patient selection has not been tested rigorously in a blinded, multi-centre study. This is particularly relevant as many single-centre studies markedly overestimate the predictive effect of dyssynchrony markers compared with studies requiring formal enrolment and blinded analysis (67). However, it does appear to provide more robust, reproducible and sensitive markers of dyssynchrony than TDI. Therefore, it is reasonable to assume that it may perform better in randomised studies, should these be performed in the future.

Given the complex and multi-faceted nature of dyssynchrony, it is likely that CRT response will be best predicted by a combination of factors—echocardiographic and clinical—rather than an isolated factor. Examples of factors that are known to influence the outcome include the aetiology of heart failure, the presence of scar and the site of the LV lead.

Conclusions

STE has emerged as a clinically reproducible method of assessing LV dyssynchrony, and observational studies have shown its potential in guiding patient selection for CRT. Measurements of dyssynchrony agree with those obtained by the longer established technique of TDI; however, STE has the advantages of relatively less angle dependence and the ability to measure strain in all three planes of cardiac motion. STE is also able to provide information on patterns of myocardial activation, thus allowing the identification of optimal LV lead positioning pre-CRT implant. The limitations of STE include the need for high-resolution images. There is also the potential for speckles to drop out of the plane during cardiac motion; however, this can be overcome by the use of 3D STE, which also allows quicker analysis compared with 2D STE. Currently, no echo technique is generally accepted or guideline-endorsed for the identification of CRT responders. This is reflected in the ESC guidelines on CRT, which do not recommend using the presence of echocardiographic dyssynchrony as a selection criterion for CRT. However, they acknowledge that a number of observational studies suggest a link between dyssynchrony and the response to CRT, with the predictive value yet to be determined in randomised trials.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.
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